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Lagomorpha as a Model Morphological System

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Due to their global distribution, invasive history, and unique characteristics, European rabbits are recognizable almost anywhere on our planet. Although they are members of a much larger group of living and extinct mammals [Mammalia, Lagomorpha (rabbits, hares, and pikas)], the group is often characterized by several well-known genera (e.g., *Oryctolagus*, *Sylvilagus*, *Lepus*, and *Ochotona*). This representation does not capture the extraordinary diversity of behavior and form found throughout the order. Model organisms are commonly used as exemplars for biological research, but there are a limited number of model clades or lineages that have been used to study evolutionary morphology in a more explicitly comparative way. We present this review paper to show that lagomorphs are a strong system in which to study macro- and micro-scale patterns of morphological change within a clade that offers underappreciated levels of diversity. To this end, we offer a summary of the status of relevant aspects of lagomorph biology.

Keywords: Lagomorpha, Leporidae, Ochotonidae, evolution, morphofunction, model organism, morphology, phylogeny

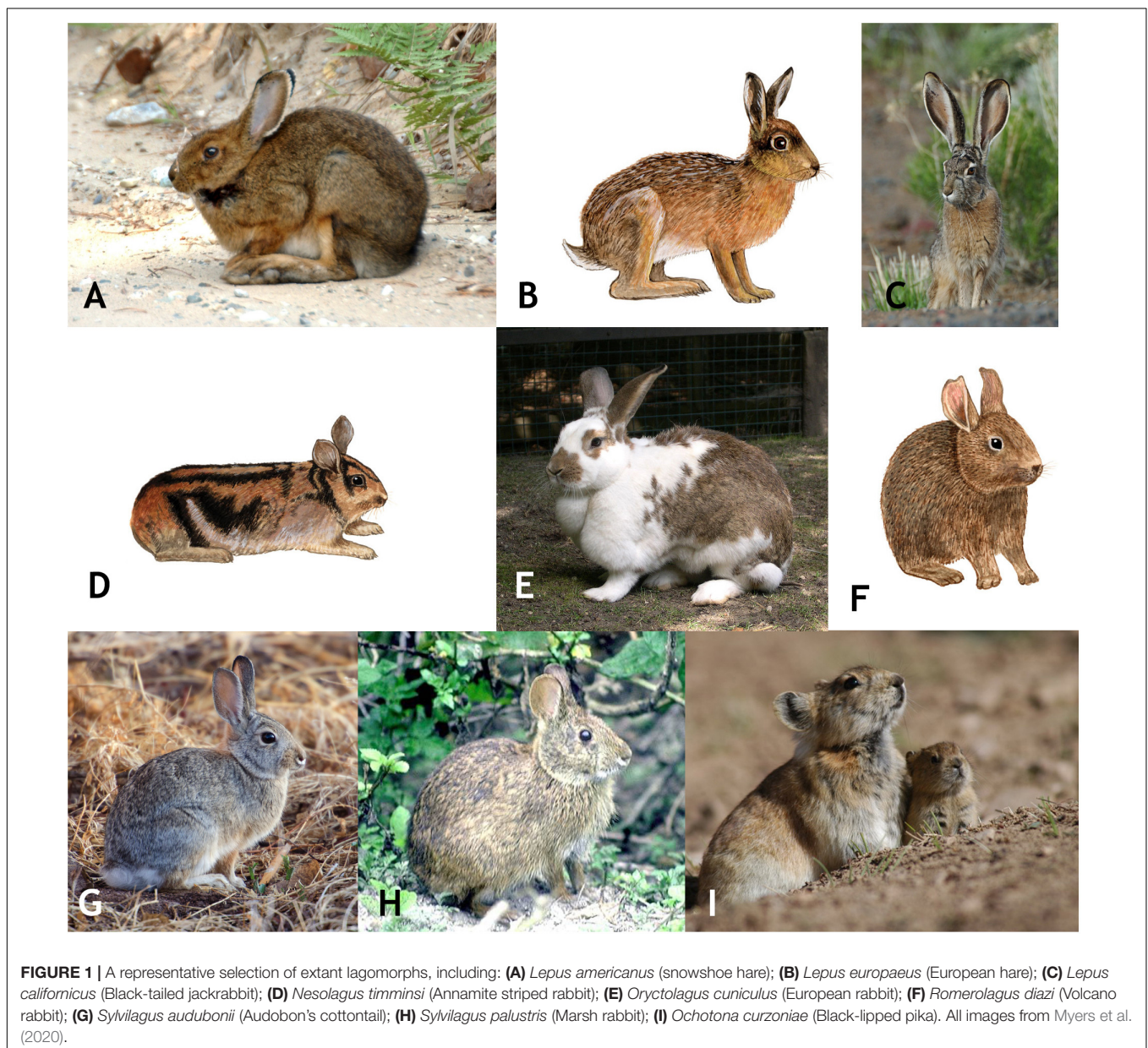## INTRODUCTION

Lagomorpha (rabbits, hares, and pikas) is a globally distributed (barring Antarctica) extant mammalian order within the larger superorder Euarchontoglires (rodents, lagomorphs, treeshrews, colugos, and primates) (Murphy et al., 2001). The order consists of herbivorous species across two extant families, the Ochotonidae (pikas) and the Leporidae (rabbits and hares) (Stock, 1976;

Forsyth et al., 2005; Hoffmann and Smith, 2005; Burgin et al., 2018; Smith et al., 2018; **Figure 1**). There are presently 12 living lagomorph genera recognized, subsuming 108 recognized species (see Burgin et al., 2018 for a recent treatment). These genera are distributed unequally between two families; the Leporidae contains 11 genera, the most well-known being *Lepus* (hares and jackrabbits), *Sylvilagus* (cottontails), and *Oryctolagus* (European rabbit) (Naff and Craig, 2012; Graham, 2015) while Ochotonidae includes only a single living genus, *Ochotona* (pikas) (Hoffmann and Smith, 2005; Ge et al., 2012; Smith et al., 2018; **Figure 2**).

Lagomorphs have featured prominently in the set of non-human model organisms that have driven many advances within the biological sciences over the last century, particularly to understand genetic, genomic, or developmental processes that drive biological change (Leonelli and Ankeny, 2013). Recent research on understanding the genome level architecture of life has included the European rabbit (*Oryctolagus cuniculus*), the mountain hare (*Lepus timidus*), the snowshoe hare (*Lepus americanus*), and the American pika (*Ochotona princeps*) (Marques et al., 2020). *Oryctolagus* and *Ochotona* have often served as the model lagomorphs in larger scale comparative studies of mammals (e.g., Sánchez-Villagra et al., 2017; Hecker et al., 2019). Though such studies have revealed much about broad patterns among mammals, often in an evolutionary context, there has been little comprehensive comparative work done within the lagomorph clade.

Monaghan (2014, p. 1019), through the lens of behavioral ecology, argue that the modern concept of model organisms

FIGURE 1 | A representative selection of extant lagomorphs, including: **(A)** *Lepus americanus* (snowshoe hare); **(B)** *Lepus europaeus* (European hare); **(C)** *Lepus californicus* (Black-tailed jackrabbit); **(D)** *Nesolagus timminsi* (Annamite striped rabbit); **(E)** *Oryctolagus cuniculus* (European rabbit); **(F)** *Romerolagus diazi* (Volcano rabbit); **(G)** *Sylvilagus audubonii* (Audobon's cottontail); **(H)** *Sylvilagus palustris* (Marsh rabbit); **(I)** *Ochotona curzoniae* (Black-lipped pika). All images from Myers et al. (2020).
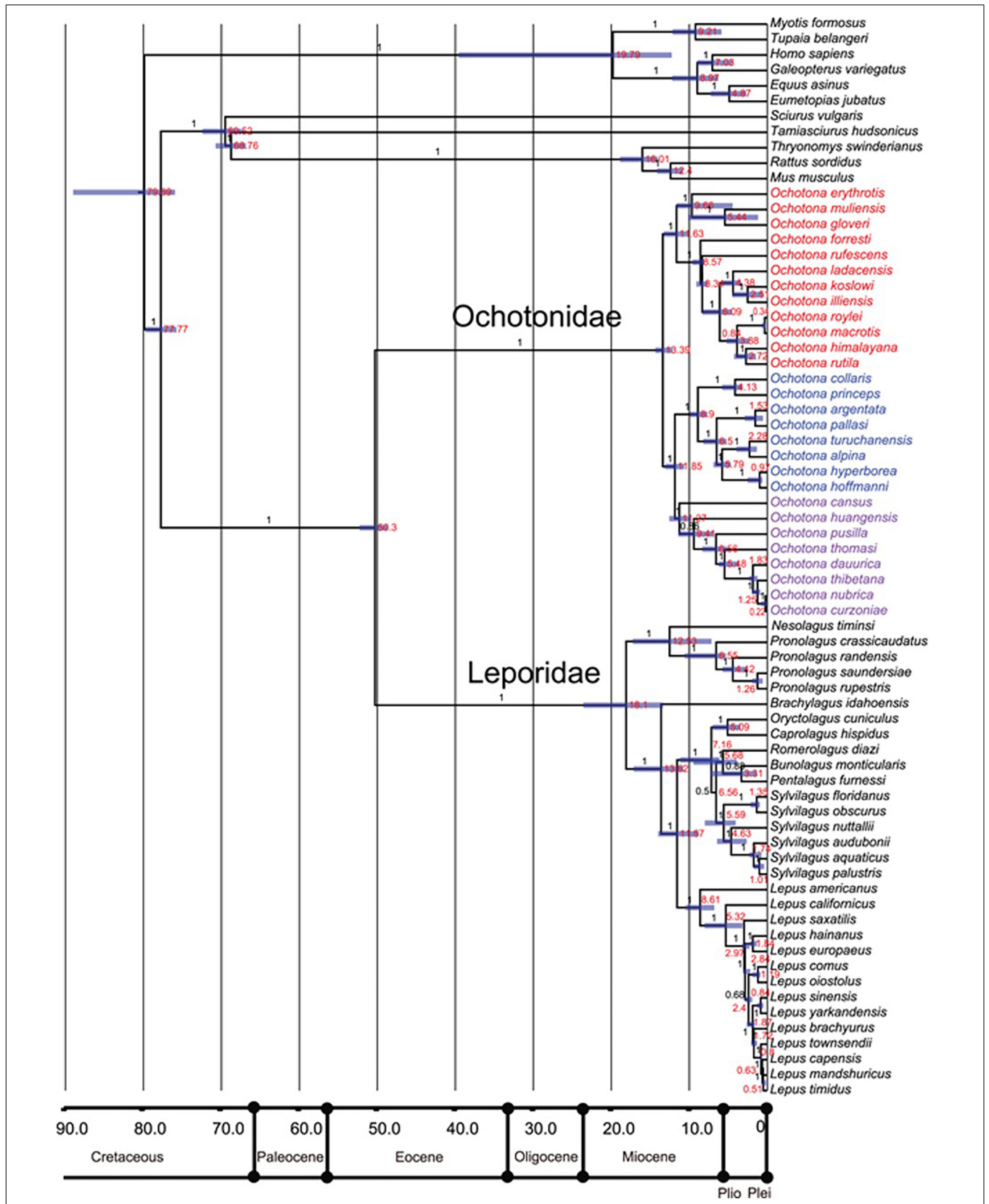
FIGURE 2 | Phylogeny of selected extant lagomorph species by Ge et al. (2013).

has limited some insights within the biological sciences away from a more intentional focus "to understand the processes responsible for the diversity that we see in animal form and function." Because such mechanisms often can be best understood by studying lineages and clades, we argue that Lagomorpha represent an ideal clade with which to explore these processes. Chapman and Flux (1990) have made such an argument for lagomorphs, which we expand here to include current scientific standings.

Among vertebrates, the radiations of anole lizards (*Anolis*) are a strong example of a clade that has served as a model system to study integrative processes in evolution and adaptive radiations (Sanger and Kircher, 2017). Extensive work on *Anolis* has included the historical, genetic, and developmental basis of anole diversity (e.g., Losos, 2011; Sanger et al., 2012; Sherratt et al., 2015; Corbett-Detig et al., 2020; Velasco et al., 2020). Though *Anolis* represents a strong comparative system, it is limited at scales that span longer geological periods. Lagomorpha are anchored by an extensively used model organism, the European rabbit (*O. cuniculus*), but include a rich fossil record that goes back to the Paleocene, a diverse group of living lineages, significant morphological and ecological disparity, and functional variation in multiple key aspects of behavioral biology. The goal of this review is to summarize key biological features of the lagomorph clade to highlight how they represent an ideal group to investigate both macro- and micro-level questions in morphological biology.

LAGOMORPH BIOLOGY

Rabbits and hares are found in forests, in open scrub, or savannah in Eurasia, Africa, and North, Central, and northern South America. Additionally, the European rabbit and hare have been introduced into Australia and South America (Chapman and Flux, 1990; Ge et al., 2013). Lagomorphs are hind-gut fermenters and require cecotrophy as well as at least a 15% crude fiber diet to maintain gastrointestinal health. Leporids are typically crepuscular and most active during the twilight hours at sunrise and sunset. They eat a wide variety of herbaceous material and grasses represent 30% of the plant food species ingested (Ge et al., 2013; Delaney et al., 2018). Pikas require a more specialized environment than hares and rabbits. They are most often found at high elevations in cold semiarid regions (Delaney et al., 2018). Pikas are distributed mainly throughout Asia, Eastern Europe, and western North America (Berkovitz and Shellis, 2018). They consume a wide variety of herbaceous plants, but grasses are a much smaller component of the diet than in that of rabbits and hares (Ge et al., 2013). The eyes of lagomorphs are laterally positioned, providing a circular field of vision (Delaney et al., 2018).

Among lagomorphs, the pikas are generally smaller (12–25 cm long; 100–400 g), with short limbs and small ears compared to their larger rabbit and hare counterparts (Ge et al., 2013; Delaney et al., 2018). Rabbits and hares have a short tail and lack or have minimal sexual dimorphism (e.g., Chapman and Ceballos, 1990; Fa and Bell, 1990; though see Orr, 1940 on sexual dimorphism in *Sylvilagus*); pikas lack an external

tail and both sexes have a cloaca-like structure and lack sexual dimorphism (Graham, 2015). Most leporid males have testes located in a scrotum in front of the penis and females possess two to five pairs of mammary glands. Embryonically, the mammary glands develop from the mammary line (ridge), as is typical for placentals. However, it was found that, in the European rabbit, the anterior pair of mammary glands appear separately above the mammary ridge, in the axilla region of the forelimb (Propper, 1976). Gestation is 21–30 days in Ochotonidae and 24–55 days in Leporidae. Ochotonidae are typically altricial, though in some species the neonates are covered with fur. Leporidae show both patterns, altricial (*Brachylagus idahoensis*, *Bunolagus monticularis*, *O. cuniculus*, and *Sylvilagus* spp.) and precocial (*Lepus* spp.) species (Lissovsky, 2016). *Pentalagus furnessi*, *Poelagus marjorita*, *Pronolagus rupestris,* and *Romerolagus diazi* are altricial as well but the young are variable with respect to fur at birth. For some rare species of *Pronolagus*, *Nesolagus* spp., and *Caprolagus hispidus*, almost no information is yet available due to their rarity (Lissovsky, 2016; Schai-Braun and Hackländer, 2016). This is representative of our anatomical knowledge of lagomorphs, while there are comprehensive treaties on *Oryctolagus cuniculus* (Krause, 1884; Bensley, 1921; Barone et al., 1973) other species are much less studied.

SYSTEMATICS

Within the 11 extant leporid genera there are approximately 75 species and 35 species in the single extant ochotonid genus, *Ochotona* (Hoffmann and Smith, 2005; Ge et al., 2012, 2013; Burgin et al., 2018). A summary of the fossil record of the Lagomorpha by Ge et al. (2013) includes about 45 genera and more than 190 species of Leporidae, and about 32 genera and 180 species of Ochotonidae (for both families, these are formally nominated taxa). The following sections highlight key features of these groups and the status of systematic relationships.

Key Craniodental Characters

Lagomorpha have been defined by a broad set of specific characters, most of which are related to mastication and locomotion, due somewhat to the relevant abundance of related osteological regions in the fossil record (e.g., López Martínez, 1985; Asher et al., 2005, 2019; Wible, 2007; Lopez-Martinez, 2008; Koenigswald et al., 2010). The living lagomorph families can be easily distinguished by several morphological characters. Besides obvious external anatomical traits such as size and shape of the outer ear and limb proportions, there exist discrete craniodental differences between the two families: e.g., proportions of the rostrum and absence or presence of fenestration and pitting of the os maxillare and bones of the posterior skull (Wood, 1940; Angermann et al., 1990; Wible, 2007). As in rodents, all lagomorphs have hypselodont (evergrowing) incisors, which are unreplaced deciduous teeth. They differ from rodents in having a second set of small permanent upper incisors. The dental formula in leporids is: I 2/1, C 0/0, P 3/2, M 3/3 with 28 total teeth and in ochotonids is: I 2/1, C 0/0, P 3/2, M 2/3 with 26 teeth (Graham, 2015; Delaney et al., 2018). See Wible (2007),

Fostowicz-Frelik and Meng (2013), and Ruf (2014) for a review of lagomorph cranial literature. Soft tissue structures such as the cephalic arterial system (Bugge, 1974) also can be used for investigation of fossil species because adjacent bony structures (e.g., foramina, sulci) serve as proxies.

In contrast, taxonomy and systematic relationships at the genus and species level, and the phylogenetic position of certain fossil taxa, remain unresolved due to possible homoplastic evolution of certain characters (Robinson and Matthee, 2005; Kraatz et al., 2010; Fostowicz-Frelik and Meng, 2013; Asher et al., 2019). For instance, the premolar foramen was regarded as a synapomorphic character of Ochotonidae although a puzzling pattern among extant Lagomorpha became evident (Corbet, 1983: lateral palatal foramen); however, a study using broad taxon sampling including fossil species clearly revealed its diversity and homoplastic nature among Lagomorpha (Fostowicz-Frelik and Meng, 2013). In his comprehensive comparative description of the external craniomandibular anatomy of *O. princeps*, *R. diazi* and further selected Leporidae, Wible (2007) complemented and refined a character matrix comprising 229 traits including 92 craniomandibular characters (Meng et al., 2003; Asher et al., 2005). To date, intracranial structures are underrepresented in phylogenetic studies of Lagomorpha. Recent studies on the nasal and ear region defined new intracranial characters that can significantly contribute to a deeper understanding of lagomorph systematics, evolution, and morphofunction. For example, extant Ochotonidae and Leporidae differ significantly in the number of turbinals (Ruf, 2014). The former have a reduced number of olfactory turbinals and lack the interturbinal in the frontoturbinal recess. The turbinal pattern in the ethmoturbinal recess of Leporidae shows certain apomorphic character states (number of ethmo- and interturbinals) in several clades that can also be used for systematic purposes at the genus and species level (Ruf, 2014).

The middle ear morphology of extant Lagomorpha reveals unique family-specific patterns of the anterior attachment of the malleus by means of the processus anterior and its processus internus praearticularis; however, the phylogenetic polarization of this character still was pending (Maier et al., 2018). A first attempt to polarize the observed patterns could be achieved by the first high-resolution computed tomography (μCT) study on intracranial structures in a fossil lagomorph; *Palaeolagus haydeni* reveals that early ontogenetic stages of *Ochotona* may represent the plesiomorphic lagomorph pattern (Ruf et al., 2021). This clearly shows the potential of μCT investigations of fossil Leporidae and Ochotonidae for elucidating the evolution of intracranial characters.

Traditionally, dental characters play a major role in lagomorph taxonomy and systematics, especially in fossil species, and there is extensive literature summarizing this important system (e.g., Dawson, 1958; Hibbard, 1963; White, 1991; Averianov and Tesakov, 1997; Patnaik, 2002; Kraatz et al., 2010; Winkler and Tomida, 2011). The occlusal pattern of anterior premolars (particularly p3) is highly diagnostic, even on a lower taxonomic level. However, although most individuals within an extant or fossil population will have the diagnostic pattern, there often are individuals (in particular, younger ones with less occlusal wear) preserving a pattern that would suggest assignment to a different

taxon (Hibbard, 1963). The masticatory pattern, also reflected in the occlusal morphology and the number of shearing blades of the cheek teeth, separates most Ochotonidae from all but two genera (*Romerolagus diazi* and *Pronolagus*) of extant Leporidae (Koenigswald et al., 2010). Beside systematic relationships and some species-specific patterns, this character complex provides insight into the evolution of functional adaptations. The lagicone structure, a complex enamel structure on the buccal occlusal surface of stem lagomorphs and certain Ochotonidae (López Martínez, 1985), becomes reduced in fossil European ochotonids; thus, the shearing function in pikas is increased. In most Leporidae the grinding function is enhanced by crenulation of specific enamel bands (Koenigswald et al., 2010). The two living lagomorph families also can be distinguished by the enamel pattern (schmelzmuster) of their incisors, a key character complex in terms of evolution and morphofunction of Glires (Martin, 1999, 2004). Generally, the incisors of Leporidae show a single-layered schmelzmuster in concert with multi-layered Hunter-Schreger bands (HSB). This pattern is derived from a double-layered schmelzmuster as observed in an undetermined leporid from the early Eocene of Kyrgyzstan and in some Mimotonidae. In contrast, Ochotonidae have a multi-layered schmelzmuster with modified HSB and enamel patterns differing in upper and lower incisors (Martin, 1999, 2004).

Key Postcranial Characters

Overall, the body-plan of lagomorphs is relatively uniform throughout their evolutionary history. There are two basic archetypes, which are represented by two extant families: the longer legged rabbits and hares, and shorter legged, rather stocky ochotonids. The ochotonid-like morphotype (or small, relatively short-limbed rabbits) dominated during the Paleogene, which suggests that true cursorial abilities appeared within lagomorphs later in the early Neogene. However, the structure of the lagomorph hindlimb with the closely connected tibia and fibula (fused already in the late Eocene *Palaeolagus*), and a unique direct calcaneo-fibular contact known from the Middle Paleocene duplicidentate of China (Fostowicz-Frelik, 2017) indicate cursorial adaptations since the groups' inception. The calcaneus is known in several Eocene lagomorphs, including the Asian *Dawsonolagus* and *Strenulagus* (Li et al., 2007; Fostowicz-Frelik et al., 2015a) and North American *Palaeolagus* (Wood, 1940). In most Paleogene lagomorphs, calcaneal structure is similar to *Ochotona*; the latter is somewhat stockier (compared to that of leporids) with a proportionally shorter tuber and calcaneal body. The calcaneal canal is a striking synapomorphy of Lagomorpha (Bleefeld and Bock, 2002).

Beginning with the Mio-Pliocene radiation, the postcranial skeleton of Leporidae acquires more cursorial adaptations. Overall, the limb bones become slenderer and the tibiofibula and foot complex (including also tarsal elements) elongate (e.g., Fostowicz-Frelik, 2007). Studies of Neogene leporid postcrania based on large samples and/or complete specimens are relatively uncommon. Most studies focus on cursorial and fossorial adaptations, for example, (1) a partial skeleton of *Trischizolagus* (early Pliocene, Moldova; Averianov, 1995) suggests it was less cursorial than *Hypolagus* and was a strong digger, although not as

fossorial as *Oryctolagus*; and (2) a large sample of *Serengetilagus* (based on forelimb anatomy; hindlimb not yet studied) ally this genus with smaller, relatively less cursorial leporids such as *Oryctolagus* and suggest it may have been semi-fossorial (early Pliocene, Tanzania; Winkler et al., 2016). As an example, from Ochotonidae, Dawson (1969) described the osteology of an abundant, albeit geologically younger (Quaternary, ca. 2.6 Ma to 200 BP) species *Prolagus sardus* from collections primarily from Corsica and Sardinia. Dawson concluded that the species "was probably not suited for speed over any great distance but was probably fairly adept at digging and well adapted for climbing and scrambling. . ." (Dawson, 1969, p. 187).

Phylogenetic Placement of Lagomorpha

The placement of Lagomorpha within the larger mammalian clade had been problematic for over a century (see Kraatz et al., 2010 for a review) due to an incomplete fossil record that did not include important stem lagomorphs. The earliest molecular phylogeny based on the eye lens protein alpha-crystallin revealed a close phylogenetic relationship of rabbits to primates (de Jung et al., 1977). That work also showed that rodents and lagomorphs form a supraordinal group (Glires) based on the interphotoreceptor retinoid binding protein (IRBP) (de Jung et al., 1977; Stanhope et al., 1992, 1996). New fossil discoveries such as the primitive rodent *Tribosphenomys* from strata of transitional Paleocene-Eocene age in Inner Mongolia (China) and Mongolia (Meng et al., 1994; Asher et al., 2005) began to support the close relationship between lagomorphs and rodents as cohort Glires. However, 91 orthologous protein sequences supported Lagomorpha as more closely related to Primates and Scandentia (treeshrews) than they are to rodents (Graur et al., 1996). The monophyly of a Glires clade was supported by complete mitochondrial genomes (Lin et al., 2002) and was consistent with the result of three nuclear studies, which included the von Willebrand Factor, an interphotoreceptor retinoid-binding protein, and an Alpha 2B adrenergic receptor (Huchon et al., 2002). Subsequently, a phylogenetic reconstruction based on 18 homologous gene segments confirmed Glires as a sister taxon to primates, colugos and treeshrews (Douady and Douzery, 2003). Analyses based on eight housekeeping genes further confirmed the monophyly of Glires (Kullberg et al., 2006). This was further evidenced by genome level data, including the monophyly of Glires, their close relationship with Primates, Scandentia and Dermoptera; and that all these taxa together formed the clade of Euarchontoglires (=Supraprimates) (Kumar et al., 2013; Foley et al., 2016; Esselstyn et al., 2017; Upham et al., 2019; Genereux et al., 2020).

Phylogenetic Relationships Within Lagomorpha

Early studies of morphological and ecological traits of extant lagomorphs resulted in different phylogenetic hypotheses (Dawson, 1981; Stoner et al., 2003). Considerable homoplasy in the morphology of leporid species was identified by Corbet (1983) after examining 21 morphological characteristics for 22 leporid species. More recent morphometric studies of

lagomorphs have also found a high degree of homoplasy, low phylogenetic signal, and adaptive divergence in skull shape (Ge et al., 2015; Kraatz and Sherratt, 2016; Feijó et al., 2020). These studies highlight the difficulties in reconstructing a robust phylogeny for lagomorphs, particularly at the intergeneric level, by using morphological data. Relationships of extant genera were reconstructed based on the combined matrix of five nuclear and two mitochondrial DNA fragments: *Ochotona* is the earliest diverging taxon, which represents a relict genus of Ochotonidae; *Nesolagus*, *Poelagus,* and *Pronolagus* form an early diverging monophyletic clade within Leporidae. *Romerolagus*, *Lepus*, *Sylvilagus*, *Brachylagus*, *Bunolagus*, *Oryctolagus*, *Caprolagus*, and *Pentalagus* form another clade of Leporidae (Matthee et al., 2004; Robinson and Matthee, 2005). The general phylogenetic structure of the tree was supported by genomic orthologous retroposon insertion sites (Kriegs et al., 2010).

Within Lagomorpha, *Lepus* and *Ochotona* represent the most speciose extant genera. Molecular phylogenies within each of these genera have been extensively studied. The early studies are generally based on a single locus mitochondrial DNA marker, cytochrome b (*CYTB*) (Yu et al., 1996; Halanych et al., 1999; Niu et al., 2004). Five major species groups within *Ochotona* were recognized: the northern group, the surrounding Qinghai-Tibet Plateau group, the Qinghai-Tibet Plateau group, the Huanghe group, and the Central Asia group (Niu et al., 2004; Lanier and Olson, 2009). Subsequently, more genes were included, for example, the dataset of *CYTB* 12S, ND4, and the control region of the mitochondrial genome revealed the Chinese hare (*Lepus sinensis*) is not a monophyletic group, with three species groups recognized within *Lepus*: North America species group, South Africa species group and the Eurasia species group (Wu et al., 2005; Liu et al., 2011). Recent studies based on exome of the whole genome supported five subgenera of extant *Ochotona*: *Alienauroa*, *Conothoa*, *Ochotona*, *Lagotona*, and *Pika*, with divergence time and phylogeographic analyses inferring the last common ancestor of extant pikas first occurred in the middle Miocene, approximately 14 Ma (Wang et al., 2020).

Mito-nuclear discordance was shown in *Lepus* (Kinoshita et al., 2019) and *Ochotona* (Lissovsky et al., 2019), which could be the result of incomplete lineage sorting, sex-biased dispersal, asymmetrical introgression, natural selection, or *Wolbachia*-mediated genetic sweeps. The genome of four lagomorph species (*O. cuniculus*, *L. timidus*, *L. americanus*, and *O. princeps*) has been sequenced and annotated (Marques et al., 2020). These data provide references for more deep level studies in exploring the morphology, behavior, as well as population genetics of lagomorphs. However, more novel sampling is still needed for a complete phylogenomic analyses of Lagomorpha. Moreover, integrating data from fossils with extant species probably will provide a more comprehensive overview on the evolutionary history of lagomorphs.

THE FOSSIL RECORD

Lagomorphs of modern aspect are known in the fossil record since the Early Eocene (ca. 52 Ma) of China (Li et al., 2007;

Wang et al., 2010) and Mongolia (Lopatin and Averianov, 2008). The Asian record of Lagomorpha precedes that of North America by over 10 million years, and that of Europe by almost 20 Ma. Asia is considered the diversification center for the Duplicidentata, treated as a more inclusive group including crown lagomorphs and species more closely related to extant lagomorphs than rodents. Many of these earliest species are characterized by a double set of the upper and lower incisors and are referred to the ancestral Mimotonidae (Meng and Wyss, 2001; Fostowicz-Frelik et al., 2015b; Fostowicz-Frelik, 2017), an extinct fossil group restricted to China, Mongolia, and Kyrgyzstan (Li, 1977; Li and Ting, 1985; Averianov, 1994; Asher et al., 2005; Li C. K. et al., 2016; Fostowicz-Frelik, 2020). The mimotonids are a paraphyletic group with two distinct lineages: the small Paleocene mimotonids (Li, 1977; Li C. K. et al., 2016; Fostowicz-Frelik, 2020) and the large Eocene forms (Bohlin, 1951; Averianov, 1994; Meng et al., 2004; Asher et al., 2005; Fostowicz-Frelik et al., 2015b). One of the large forms, *Mimolagus*, likely survived to the Eocene–Oligocene boundary (Bohlin, 1951; see also Zhang and Wang, 2016) and was the terminal representative of the mimotonids (Fostowicz-Frelik et al., 2015b). Although Lagomorpha and Mimotonidae share many similarities in dental structure, most of these characters are plesiomorphic; thus, none of the mimotonids could be unquestionably named the direct ancestor of lagomorphs. All the Eocene lagomorph taxa and a substantial part of the Oligocene species are regarded as stem lagomorphs, although they frequently show similarities to either of the crown groups (Leporidae and Ochotonidae, see Fostowicz-Frelik and Meng, 2013).

The earliest findings of non-mimotonid stem lagomorphs come from the latest Early Eocene of Asia: *Dawsonolagus* from Inner Mongolia, China (Li et al., 2007), and *Arnebolagus* from Mongolia and Kyrgyzstan (Averianov and Lopatin, 2005; Lopatin and Averianov, 2008, 2020). By the Middle Eocene, China and Kyrgyzstan witnessed the first lagomorph diversification, yielding multiple genera (Li, 1965; Tong, 1997; Averianov and Lopatin, 2005; Meng et al., 2005; Fostowicz-Frelik et al., 2012, 2015a; Fostowicz-Frelik and Li, 2014; Li Q. et al., 2016). By the end of the Eocene, the lagomorph fauna of Asia was enriched, in particular, by *Desmatolagus* (Meng et al., 2005), a key lagomorph genus for the Oligocene in Asia (Erbajeva and Daxner-Höck, 2014).

Asian Eocene lagomorphs were very small, with an estimated body mass under 150 g (Fostowicz-Frelik et al., 2015b). Starting from the Middle Eocene, Asian lagomorphs doubled in size, but even then, most of the Paleogene genera did not exceed the size of a large *Ochotona* (ca. 250 g). With the beginning of the Oligocene, the *Desmatolagus* lineage became diverse, abundant, and widespread throughout Central Asia (Sych, 1975; Huang, 1987; Wang, 2007), surviving until the Miocene, and possibly entering Europe (Early Oligocene, Vianey-Liaud and Lebrun, 2013) and North America (Late Oligocene; Dawson, 2008). Along with *Desmatolagus*, in the late Early/Middle Oligocene, the first plausible representatives of crown lagomorphs appear in Asia: *Sinolagomys* (an early ochotonid from China and Mongolia; see Erbajeva et al., 2017) and *Ordolagus* (probably an early leporid from China; Bohlin, 1942).

In North America, the lagomorph fossil record starts in the late Middle Eocene (ca. 42 Ma; see Dawson, 2008). Two genera, *Mytonolagus* and *Procaprolagus*, are known from this period and likely represent two different immigrations from Asia (Dawson, 2008). There is a significant increase in diversity in the Lagomorpha of North America beginning in the Late Eocene: this includes genera with true hypselodont cheek teeth such as *Chadrolagus* (Gawne, 1978; Fostowicz-Frelik, 2013) and the first representatives of *Palaeolagus* and *Megalagus* (Dawson, 1958, 2008). At the Eocene-Oligocene boundary (EOB), a turnover in the lagomorph fauna is observed, defined by a shift from unilateral hypsodonty (i.e., high-crowned, evergrowing lingual sided and low-crowned buccal sided cheek teeth) toward a hypselodont condition in their cheek teeth ('full' hypsodonty). Among *Megalagus* and *Palaeolagus*, the unilaterally hypsodont species went extinct at the EOB and were replaced by species either with greatly reduced buccal roots, or fully developed hypselodont cheek teeth. *Litolagus*, with its advanced cranial morphology, may represent either crown Leporidae (see Fostowicz-Frelik, 2013) or an advanced stem taxon. Later during the Early Oligocene, other hypselodont species appear, for example, *Palaeolagus burkei* may be closely related to *Litolagus* or it may have convergent traits in dentition and bulla structure, which could be a result of adaptations to more open habitats of the North American plains. All lagomorph lineages that originated during the Eocene-to-Oligocene interval in North America went extinct by the Early Miocene (Dawson, 2008).

In Europe, the earliest lagomorphs are known from the Early Oligocene of France (*Ephemerolagus nievae*; Vianey-Liaud and Lebrun, 2013) and Germany (*Shamolagus franconicus*; Heissig and Schmidt-Kittler, 1975, 1976). The remains are scarce, and their appearance is limited only to the type localities, but these genera clearly represent two distinct lineages. Lagomorph lineages reappearing in Europe by the end of the Oligocene (Tobien, 1974, 1975) are regarded as either primitive ochotonids (McKenna, 1982) or as stem line representatives (Fostowicz-Frelik and Meng, 2013). These lineages persist in Europe from the Late Oligocene (Fostowicz-Frelik, 2016) until the Early Miocene (Tobien, 1974).

The Early to Middle Miocene (beginning ca. 23 Ma) is characterized by the last records of the stem lagomorphs and the worldwide radiation of the Ochotonidae (Dawson, 2008; Ge et al., 2013). The Early Miocene record of stem Lagomorpha consists mostly of derived *Desmatolagus* (Lopatin, 1998; Wang et al., 2009) and Asian representatives of *Amphilagus*, a Late Oligocene-Early Miocene genus from Europe, which has been reported recently also from Mongolia and Siberia (Erbajeva, 2013; Erbajeva et al., 2016). In North America, the earliest Miocene marks the last appearance of taxa such as *Megalagus* and *Palaeolagus* (Dawson, 2008). In Europe a plethora of Ochotonidae appeared in the Early Miocene, for example *Alloptox* and *Prolagus* (Tobien, 1974, 1975; López Martínez, 2001). In the Early and Middle Miocene taxa such as these existed alongside the stem lineages, which went extinct no later than the Middle Miocene (Tobien, 1974; Fostowicz-Frelik et al., 2012). *Prolagus*, first reported from the Early Miocene, was the most speciose and long-lived lineage of the European ochotonids and the last

species, *P. sardus*, survived in the Mediterranean until historic times (Lopez-Martinez, 2008). Simultaneously, starting from the Middle Miocene, a lineage leading to extant *Ochotona*, the only surviving member of the Ochotonidae, arose in Central Asia (Wang et al., 2009; Fostowicz-Frelik and Frelik, 2010): this lineage also flourished in Asia during the Pliocene.

The earliest known ochotonids from North America are from near the Oligocene-Miocene boundary: all these early immigrants went extinct not later than ca. 9 Ma (Dawson, 2008). *Ochotona* was first reported in North America in the Late Miocene: this genus was geographically and taxonomically diverse during the Late Miocene-Pliocene in the Northern Hemisphere (Erbajeva et al., 2015). The genus decreased in diversity and relative abundance beginning in the Pleistocene (ca. 2.6 Ma; Erbajeva et al., 2015).

The earliest lagomorphs to reach Africa were representatives of the Asian sinolagomyine ochotonids, which dispersed into Africa as far as southern Africa in the Early Miocene (Winkler and Avery, 2010). Extinction of the African sinolagomyines by the Middle Miocene was coincident with the global extinction of archaic ochotonids by the end of the Middle Miocene (Erbajeva et al., 2015). The only post Middle Miocene reports of ochotonids from Africa are *Prolagus*, reported from the Late Miocene to Early Pleistocene of northern Africa (López Martínez, 2001; Winkler and Avery, 2010). In contrast to the ochotonids, Ge et al. (2013) noted that the diversity of the Leporidae was relatively modest during much of the Miocene, increasing around the Miocene-Pliocene transition, and with high diversity continuing into the Pliocene and Pleistocene.

The earliest record of leporids in Africa is in the Late Miocene (Winkler and Avery, 2010) as part of a geographically widespread and relatively abrupt dispersal of leporids at ca. 8 Ma that Flynn et al. (2014) called the Leporid Datum. Leporids dispersed from North America to northern Asia, spread throughout Eurasia, and entered Southern Asia (by 7.4 Ma) and Africa (ca. 7 Ma) (Flynn et al., 2014). Ge et al. (2013) correlated the geographic dispersal and increase in diversity of the leporids around the Late Miocene (and the opposite response of the ochotonids) with a period of global cooling and drying, and the expansion and diversification of C4 plants (at the expense of the C3 plants) in tropical and temperate areas.

KEY FUNCTIONAL GENES OF LAGOMORPHS

Wild populations of lagomorphs are greatly affected by two diseases, rabbit hemorrhagic disease and myxomatosis. The genes relating to the immune system and these diseases are well studied. These are, for example, interleukins, chemokines and chemokine receptors, Toll-like receptors, antiviral proteins (RIG-I and Trim5), and the genes encoding fucosyltransferases that are utilized by rabbit hemorrhagic disease virus as a portal for invading host respiratory and gut epithelial cells (Pinheiro et al., 2016). Fourteen IgA (immunoglobulin A) subclasses have been identified in *O. cuniculus*, eleven of which are expressed. In contrast, most other mammals have only one IgA, or in the

case of hominoids, two IgA subclasses (Pinheiro et al., 2018). VHn genes are a conserved ancestral polymorphism that has been maintained in the leporid genome and being used for the generation of VDJ rearrangements by both modern *Lepus* and *Oryctolagus* (Pinheiro et al., 2019). Toll-like receptors (TLRs) are one of the first lines of defense against pathogens and are crucial for triggering an appropriate immune response: strong selection of the TLR2 coding region among the Lagomorpha suggests an evolutionary history that differs from other mammals (Neves et al., 2019). A high level of variation in the tripartite motif-containing protein 5 alpha (TRIM5) PRYSPRY domain of Lagomorpha species that belong to the same genus was believed to restrict retroviral infections (Águeda-Pinto et al., 2019). Recent study revealed the winter coat color polymorphism of snowshoe hares was associated to the genomic region of the pigmentation gene Agouti (Giska et al., 2019; Jones et al., 2020). Genetic variation at Agouti clustered by winter coat color occurs across multiple hare and jackrabbit species (Jones et al., 2018).

HYBRIDIZATION IN LAGOMORPHA

Hybridization may accelerate speciation via adaptive introgression or cause near-instantaneous speciation by allopolyploidization (Abbott et al., 2013). There are many articles referring to the hybridization, gene flow or reticulate evolution of lagomorphs (**Table 1**). Previous studies reported hybridization occurred within *Lepus*, *Oryctolagus*, and *Ochotona* usually based on single, multilocus DNA markers, and microsatellite loci (Chapman and Morgan, 1973; Wu et al., 2011; Koju et al., 2017). In some cases, selective advantages of hybrid forms to special climate condition in the contact zone and competitive exclusion of parental forms causes hybrid superiority over parental species (Mohammadi et al., 2020) because enhanced reproductive success may be due to the selective advantages of new combinations of mito-nuclear packages.

In addition, transitional phenotype of hybrids and introgressions also encounter traditional taxonomy with confusion in hybrid zones while reticulate and mosaic evolution of the genome and incomplete lineage sorting especially within nuclear loci also make application of new molecular tools such as DNA barcoding for identification of species useless. Plausible conspecificity have been raised from lack of morphological diagnostic characters and low genetic divergence in phylogenetic reconstructions based on some few nuclear loci (Liu et al., 2011). There are still gaps in sampling from type localities of some taxa (e.g., *Lepus tibetanus pamirensis*; type locality: near Lake Sarui-Kul, Pamir Mountains) and gaps for understanding the intraspecific genetic diversity (e.g., in *Lepus saxatilis* from Africa, in *Lepus melainus* and all other kinds of Manchurian hares). The taxon *przewalskii* is still controversial and the taxonomic status of *centrasiaticus* has not been resolved due to its morphological similarities to *Lepus oiostolus*, and its morphometric (Cheng et al., 2012) and molecular affinity to *L. tolai* (Wu et al., 2011; Smith et al., 2018). Possible paraphyly of some taxa such as *L. timidus* and *Lepus tolai* in China (Wu et al., 2005; Shan et al., 2020); *Lepus capensis s.l.* in Africa

TABLE 1 | Research activities related to hybridization of Lagomorpha.

Species	Data	Major conclusion	References
L. granatensis L. europaeus L. castroviejoi L. corsicanus L. timidus L. capensis L. arcticus L. othus L. americanus L. californicus L. townsendii	14 nuclear DNA and 2 mtDNA fragments	Highly incongruent with mtDNA phylogeny using parametric bootstrap. Simulations of mtDNA evolution under the speciation history inferred from nuclear genes did not support the hypothesis of mtDNA introgression from L. timidus into the American L. townsendii but did suggest introgression from L. timidus into four temperate European species.	Melo-Ferreira et al., 2012
L. europaeus L. granatensis	Autosomal microsatellite loci and X- and Y-linked diagnostic loci	The lack of mtDNA differentiation across the boundary is mostly due to sharing of mtDNA from a boreal species currently extinct in Iberia (L. timidus) whose mitochondria have thus remained in place since the last deglaciation despite successive invasions by two other species.	Melo-Ferreira et al., 2014a
O. cuniculus algirus O. c. cuniculus	Transcriptome and the target enrichment datasets	Genes lying within differentiated regions were often associated with transcription and pigenetic activities, including chromatin organization, regulation of transcription, and DNA binding.	Carneiro et al., 2014
L. americanus L. townsendii L. californicus	Eight nuclear markers and one mitochondrial DNA	The isolation-with-migration model suggested that nuclear gene flow was generally rare or absent among species or major genetic groups, coalescent simulations of mtDNA divergence revealed historical mtDNA introgression from L. californicus into the Pacific Northwest populations of L. americanus.	Melo-Ferreira et al., 2014b
L. granatensis L. timidus	100 nuclear SNPs	The distribution of allele frequencies across populations suggests a northward range expansion, particularly in the region of mtDNA introgression.	Marques et al., 2017
O. spp.	Two mitochondrial (CYT B and COI) and five nuclear gene segments (RAG1, RAG2, TTN, OXAIL and IL1RAPL1)	Conflicting gene trees implied mitochondria introgression from O. cansus to O. curzoniae.	Koju et al., 2017
L. timidus L. europaeus	6833 SNP markers	Introgression is highly asymmetrical in the direction of gene flow from mountain hare to brown hare, and that the levels of nuclear gene introgression are independent of mtDNA introgression.	Levanen et al., 2018
L. americanus	Whole genome sequence	Genetic variation at Agouti clustered by winter coat color across multiple hare and jackrabbit species, revealing a history of recurrent interspecific gene flow.	Jones et al., 2018
O. princeps	24 microsatellite loci	Fine-scale population genetic analysis suggests gene flow is limited but not completely obstructed by extreme topography such as glacial valleys, as well as streams including the Colorado River.	Castillo Vardaro et al., 2018
L. timidus L. granatensis	Whole genome sequencing	Post-glacial invasive replacement of L. timidus by L. granatensis. Outliers of elevated introgression include several genes related to immunity, spermatogenesis, and mitochondrial metabolism.	Seixas et al., 2018

(Lado et al., 2016) and *L. timidus* from northern Europe, Siberia, and Fennoscandian regions (Waltari and Cook, 2005) add to the complexity of the taxonomic status of some of the members of the genus *Lepus* and essential need for revision based on complete genome phylogenetic analyses. There are many reports of hybridization between different species like between *L. tolai,* and *L. timidus* with *L. sinensis*, from *L. sinensis* into *L. mandshuricus* (Liu et al., 2011), between *L. tolai* and *L. yarkandensis* (Wu et al., 2011), *L. timidus* into *L. granatensis* and *L. europaeus* (Alves et al., 2003), from *L. europaeus* into *L. tolai* (Mohammadi et al., 2020). Sharing of the same haplotypes between two different species and some cases of hybridization and introgression between sister taxa have been also reported within pikas [e.g., between *Ochotona cansus* and *Ochotona curzoniae* (Koju et al., 2017), *Ochotona dauurica* and *O. cansus* (Lissovsky et al., 2019), *O. curzoniae* and

Ochotona nubrica (Yu et al., 2000; Niu et al., 2004; Lissovsky, 2014; Lissovsky et al., 2019)]. Moreover, lack of type specimens and the probable presence of hybrid forms even in the type localities, which makes molecular comparisons doubtful (e.g., for *L. tolai*; see Mohammadi et al., 2020) and have raised even further questions concerning the taxonomy and evolutionary relationships between taxa. More comprehensive studies are needed to address taxonomic challenges remaining around the North American white-tailed jackrabbit *Lepus townsendii*, *Lepus corsicanus* from Italy, and *Lepus castroviejoi* from the Iberian Peninsula.

The vast variety of introgression and evidence of hybridization between two species in areas of sympatry and parapatry (e.g., between *L. europaeus* and *L. tolai* in Iran; *L. europaeus* and *L. timidus* in Sweden; *L. tolai* and *L. yarkandensis* in Tarim Basin, China) and the lack of evidence of hybridization in other cases

of geographical sympatry (e.g., between *L. europaeus* and *L. tolai* in Kazakhstan; between *L. tibetanus*, *L. oiostolus*, and *L. tolai* in China; *L. yarkandensis* and *L. timidus* also in China) have suggested the genus *Lepus* as a good natural model for studying and tracing hybridization and the speciation process and also highlights the insufficient taxonomic knowledge to identify many of the taxa indicated as hybridized in scientific literature.

DOMESTICATION OF LEPORIDAE

The domesticated rabbit is derived from *O. cuniculus* and has its history in early European cultures (Clutton-Brock, 1989). While it is hypothesized that the Romans spread wild rabbits out of the native Iberian Peninsula to much of Europe and British Isles, they did not attempt to domesticate it. Several authors recounting the history of rabbit domestication place the origin with French Medieval monks (Clutton-Brock, 1989; Naff and Craig, 2012), where rabbits were kept in hutches or walled gardens to be fattened up for consumption, and thus selectively bred to increase body size. The morphological diversity among the ∼50 breeds of the domesticated rabbit known today is driven by body size (e.g., dwarf and giant forms), thus many differences in morphological features are likely a result of allometry, the associated shape changes with size, and heterochrony, the changes in timing of development (e.g., Fiorello and German, 1997; Sánchez-Villagra et al., 2017). Studies of morphological variation in companion and laboratory rabbits are predominantly focused on pathological and skeletal abnormalities resulting from their continual tooth growth (e.g., Okuda et al., 2007; Böhmer and Böhmer, 2017; Parés-Casanova and Cabello, 2020).

LAGOMORPH DEVELOPMENT

Our knowledge of lagomorph development is based primarily on the common laboratory rabbit, *O. cuniculus*, because this species is easy to keep and breed and therefore early ontogenetic stages are readily available. *O. cuniculus* is an induced ovulator (Boussit, 1989; Delaney et al., 2018). Sexual differentiation is established on the 16th day of embryonic development, and oogenesis continues for about 2 weeks after birth (Mauleon, 1967; Kennelly et al., 1970). Graafian follicles appear in the New Zealand breed at 12 weeks of age. Ovulation occurs between 10 and 12 h after mating and the peak of fecundity is observed between 12 and 15 h *post coitum* (*pc*) (Harper, 1961; Thibault, 1967; Foote and Carney, 2000). Based on the observations of Lopez-Bejar (1995), embryos have completed their first cell cycle at 26 h *pc*, then continue to divide to reach the 4-cell stage at 26–32 h *pc*, followed by 8-cell (32–40 h *pc*), 16-cell (40–47 h *pc*), morula (47–68 h *pc*), and blastocyst (68–76 h *pc*) stages. The embryo begins to implant 7 days after fertilization (DeSesso, 1996). The blastocyst loses its zona pellucida, which is replaced by layers of glycoproteins whose adhesive properties play an important role in implantation (Alliston and Pardee, 1973). The ectoblast covers a deep layer or endoblast. A medium or mesoblast layer is isolated between the two previous layers. The embryo begins to lie down on the 8th day of gestation; then on the 11th day the head becomes dominant in size and the limbs lengthen. From the 19th day (end of organogenesis), the limbs are well formed, and the muzzle lengthens. From 12th day of gestation, development of the bi-discoid and hemochorial placenta will ensure the growth and development of the fetus until parturition (Rodriguez et al., 1985). The weight of the young rabbits does not change much until the 16th day but then increases very quickly: between 24th and 30th day, the rabbit fetus multiplies its weight by six (Bruce and Abdul-Karim, 1973). Gestation is from 30 to 33 days.

Understanding the development of the mammalian cranium requires the investigation from early prenatal to adult stages (Gaupp, 1906; Novacek, 1993; Maier and Ruf, 2014). These data provide the ultimate baseline for character polarization and a deeper understanding of ontogenetic transformations into adult stages and thus, significantly contribute to comparative anatomical, morphofunctional, systematic and evolutionary studies (e.g., Maier and Ruf, 2014; Sánchez-Villagra and Forasiepi, 2017; Ruf, 2020). To date models of cranial development in Lagomorpha are still mainly based on *Oryctolagus cuniculus* (e.g., Voit, 1909; de Beer and Woodger, 1930; Frick and Heckmann, 1955; Hoyte, 1961) because access to ontogenetic series is easy. Only a few other species are known by pre- or perinatal stages, although their cranial development has not been studied in as much detail. These are: *L. capensis* (Eloff, 1950), *Ochotona rufescens* and *Ochotona roylei* (Insom et al., 1990), and *Ochotona* sp. (Frahnert, 1998). However, all these studies comprise single or very few stages that were prepared as histological serial sections. Postnatal ontogeny of the lagomorph cranium has been mainly investigated based on osteological features, for instance, skull size and shape changes in *O. curzoniae*, *L. oiostolus*, and *L. capensis* (Lu, 2003; Zhang and Ge, 2014), growth of the ear capsule in *O. cuniculus* (Hoyte, 1961). Regarding cranial development, Lagomorpha, and especially Leporidae, can be the ideal model organism because they comprise different modes of reproduction (altricial, precocial) that help to elucidate developmental and evolutionary constraints in lagomorph evolution. The ontogenetic transformation of cranial features in altricial versus precocial species provides key features to character polarization and transformation serving as baseline for the understanding of systematics, morphofunction, and evolution of the respective species and clades. This has been attempted recently by the study of perinatal dental eruption in selected Glires (including *O. cuniculus* and *L. europaeus*) or the comparison of chondrocranial transformations in altricial and precocial Muroidea (Ruf, 2020; Ruf et al., 2020).

Comprehensive studies of the cranial development in selected lagomorph species that include ontogenetic series spanning from fetal to adult are still pending, although sufficient material of selected species is certainly available in scientific collections. This approach is essential to understand cranial characters and adult patterns, as demonstrated by a recent study on the auditory ossicles in lagomorphs (Maier et al., 2018). Based on both histological serial sections of perinatal stages and μCT scans of adult skulls of Ochotonidae and Leporidae, Maier et al. (2018) revealed a family-specific pattern of the

processus anterior and processus internus praearticularis of the malleus. The perinatal stages provide insight into the development of the two very different adult patterns that correlate with adaptations in sound transmission and allow for refining previous functional classifications of mammalian auditory ossicles (Maier et al., 2018).

## New Methods in Assessing Development

The cranial anatomy and development of prenatal to early postnatal stages in mammals traditionally have been investigated using histological serial sectioning (Hall, 2005). Although this method is destructive and time consuming it allows the detailed study of hard and soft tissue structures and has led to important observations regarding the development of soft tissue (e.g., Maier et al., 2002; Ruf et al., 2009). Advances in modern imaging techniques such as μCT, allow for non-destructive investigation of any ontogenetic stage, as well as rare, collection specimens. Promising new diffusion based methods that increase the radio-opacity (and thus contrast) of soft tissues in specimens prior to μCT scanning are becoming more widespread and represent a frontier in the study of development in a wide variety of taxonomic groups (Metscher, 2009a,b; Gignac et al., 2016). Phosphotungstic acid and inorganic iodine are the two stains that are becoming increasingly common research tools; they are relatively easy to handle and produce high-contrast X-ray images of many soft tissues. Iodine (IKI and I2E) staining followed by μCT scanning works particularly well with mammals, including lagomorphs (Racicot and Ruf, 2020; **Figure 3**) and also is reversible using simple destaining methods. Specimens still may be processed for histological staining and sectioning or other methods after μCT scanning, and thus provide a record of their original internal and external three-dimensional geometries prior to employing subsequent destructive methods.

While μCT scanning has become a standard method for paleontologists, biologists, and museum researchers (e.g., Racicot, 2017), using staining to increase radio-opacity before

μCT scanning still is a relatively new approach. Some general guidelines and examples of success with iodine staining and scanning methods are described in the literature (summarized in Metscher, 2009a,b; Gignac et al., 2016). Iodine provides clear contrast between neural and other tissues because its inner shell electron binding energy is similar to lower energy X-rays used in scans and often is used in medical contexts.

The most conservative methodology for rare museum specimens has been exemplified by recent work on cetaceans (Lanzetti et al., 2018) and tested with a prenatal stage of a lagomorph (**Figure 3**). Specimens that are preserved in formalin may be directly placed either in pre-prepared or self-prepared ~1% Lugol's iodine solution (e.g., **Figure 3**). For specimens preserved in 70% alcohol, metal iodide is mixed first in the highest alcohol concentration possible (96–100%), then diluted to 70% alcohol with iodine before beginning staining. Rotating or moving the specimens either constantly or daily while staining is recommended because the stain can settle.

Other staining methods have been employed but may not work well with larger specimens. Phosphotungstic acid can be used effectively, particularly after fixation with Bouin's solution, but penetration times are slower than iodine methods, and it is unclear whether this method is reversible (Metscher, 2009a,b). It has been suggested that specimens fixed in Bouin's solution and preserved in 70% alcohol can be stained with I2E before μCT scanning (Metscher, 2009b) for effective increase in contrast. After the staining and scanning process is completed, specimens can be destained using 3% sodium thiosulfate dissolved in deionized water (for formalin specimens) or 70% ethanol (for ethanol specimens). The specimen subsequently can be used for future research, including re-staining and/or sectioning as desired. It is recommended to note in the documentation associated with the specimen that the specimen has been stained and μCT scanned previously. Some workers have noted that DNA perhaps should not be extracted from specimens after this procedure (Gignac et al., 2016) because the impact of staining on
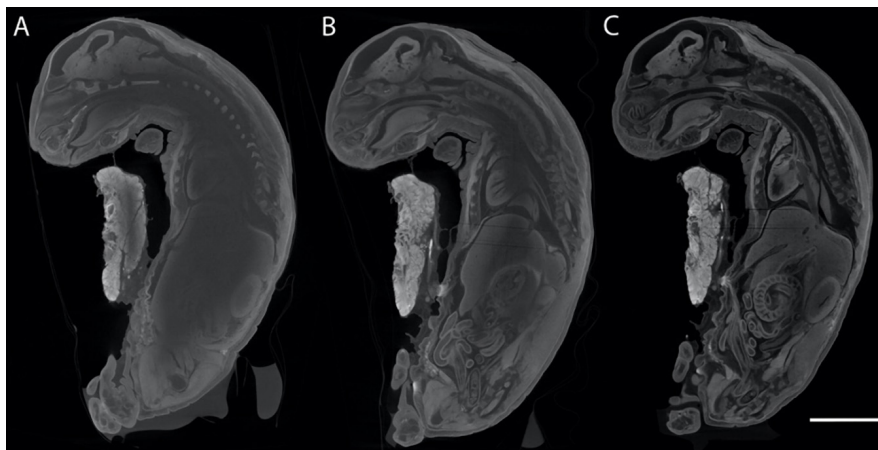
FIGURE 3 | Sagittal μCT slices taken from generally the same area of the same *O. cuniculus* specimen (Racicot and Ruf, 2020), stained for different lengths of time to show increasing contrast imparted by the Lugol's iodine stain. **(A)** Stain penetration after 5 weeks and 2 days, **(B)** penetration after 7 weeks, **(C)** stain penetration after 11 weeks and 2 days. Scale bar of 10 mm applies to all specimens.
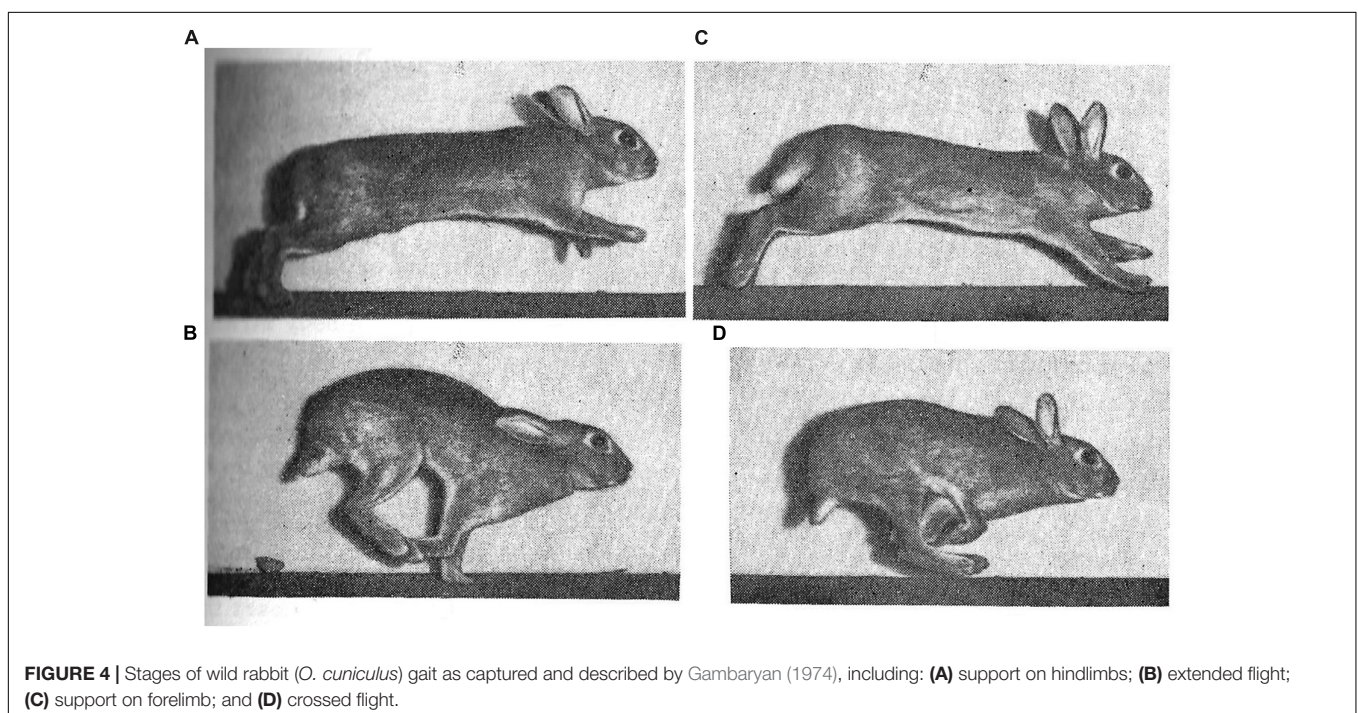
DNA analyses has not been explored: experiments along these lines thus may be interesting. μCT scanning in combination with iodine staining represents a promising frontier in studying the development and ontogeny of lagomorphs, particularly in rare species/museum specimens for which destructive methods are unattractive options. Maintaining the 3D geometry of soft tissues, while also 'remotely' observing these tissues with high contrast will increase the natural history value of the specimens by providing a permanent digital record that can also be used in educational contexts.

FUNCTIONAL MORPHOLOGY

Leporids are characterized by increased cursoriality, in general; pikas are the least cursorial and jackrabbits the most cursorial, with rabbits and cottontails (e.g., *Sylvilagus*) occupying an intermediate position (Camp and Borell, 1937; Gambaryan, 1974). A small number of previous studies have discussed the gradation in cursoriality among lagomorphs and sought to identify morphological correlates of this behavioral cline (Camp and Borell, 1937; Gambaryan, 1974; Bramble, 1989; Kraatz and Sherratt, 2016). Among lagomorphs, leporids are perhaps best known for their gait, in which maximum running speeds of some species match the upper limit of racehorses and greyhounds; a speed unknown for any other mammal of leporid size. Leporid speeds vary from 40 km/h (11 m/s) in *Sylvilagus* through 56 km/h (16 m/s) in *O. cuniculus* and up to 72 km/h (20 m/s) in *L. europaeus* and *Lepus alleni* (Garland, 1983). While leaping abilities are common among most leporid lineages, they are also known to be facultatively semiaquatic, scansorial, fossorial, or exhibit a more generalized, non-hopping form of locomotion (Chapman and Flux, 1990). The most comprehensive framework for understanding lagomorph locomotion and locomotor apparatus in an evolutionary perspective was proposed by Gambaryan (1974), who suggested that lagomorphs originated as talus-dwellers and, therefore, regarded ochotonids as living fossils (**Figure 4**). The coupled half-bound action of the hindlimbs in lagomorphs is suggested to be the adaptative remnant of leaping from rock to rock. Among the variety of quadrupedal asymmetrical gaits in mammals, Gambaryan (1974) distinguishes two main categories: (1) true gallops, including the lagomorph half-bound and (2) 'the primitive ricochet.' The latter should not be confused with bipedal ricochet (i.e., proper hopping) of kangaroos and jerboas. According to Gambaryan (1974), the primitive ricochet is retained by many poorly running mammals, including most of the rodents.

The main difference between the true gallop and the primitive ricochet is the pattern of hindlimb motion during the extended suspension. In the primitive ricochet hindlimbs start protraction immediately as they finish their thrust and lose contact with the ground. In contrast, in the true gallop, there is a considerable delay in the hindlimb protraction where hindlimbs are held in retracted position from the end of their contact phase and throughout the extended suspension. The hindlimbs protract in gallop (e.g., lagomorph half-bound) when the forelimbs are landed; the forward swing of the hindquarters is much faster than in the primitive ricochet. According to Gambaryan (1974), the advantage of the hindlimb delay is the ability of an animal to arrive at the landing point more precisely when the hindlimbs are held fixed during a leap. Landing precision is crucial on irregular substrates such as tree branches and rocks, but also, the hindlimb delay would likely be advantageous while covering obstacles

FIGURE 4 | Stages of wild rabbit (*O. cuniculus*) gait as captured and described by Gambaryan (1974), including: **(A)** support on hindlimbs; **(B)** extended flight; **(C)** support on forelimb; and **(D)** crossed flight.

at high speeds. Gambaryan (1974) summarized lagomorph locomotor patterns as a dorsomobile-metalocomotor type. While a metalocomotor type implies the prevalence of the hindlimbs, dorsomobile implies an additional active usage of the spine; more exactly, the use of lumbar region. Lagomorphs not only actively extend their spine with hindlimb thrust, but also flex their spine when the forelimbs are landed, and the hindquarters need to be rapidly protracted.

Recording Lagomorph Gaits

The first image sequences of lagomorph locomotion were recorded as early as in 1893–1894 by Étienne-Jules Marey, which capture a very slow half-bound of the white domestic rabbit (*O. cuniculus*)[1]. However, images from those movies were not included as illustrations in his subsequent publications (Marey, 1894, 1901). This is likely why Pablo Magne de la Croix, an Argentinean Frenchman who was among the first to study the evolution of quadrupedal gaits, had an incorrect impression on the rabbit's gait (Magne de la Croix, 1928, 1933, 1936); he only depicted an extended (centrifugal) suspension, and no gathered (centripetal) suspension stage in the locomotor cycle of the rabbit. The former is characterized by the straightened spine, retracted hindlimbs and protracted forelimbs, while in the latter the spine is flexed, the hindlimbs are protracted and cross the retracted forelimbs. In rabbits, with speed growth, there is at first no suspension in the locomotor cycle, then the gathered suspension appears (missed by Magne de la Croix), and finally the extended suspension is added (not recorded by Marey). Both stages of suspension were recorded by Gambaryan (1974) in the wild European rabbit 80 years after Marey's first observations. Also, Gambaryan's (1974) work was the first publication representing the frames of cinematographic record of the running cycle of the Alpine pika (*Ochotona alpina*). He noted that in pika the gathered suspension is almost absent, but the extended stage is prolonged to ensure leaping from stone to stone in their usual rocky habitat.

After Marey (1894, 1901) and Gambaryan (1974), there appeared in scientific publications a few additional illustrations of running lagomorphs. Dimery (1985) filmed wild rabbits at a high frequency (300 frames per second) but depicted only the outlines of the hindlimb movements. Bramble (1989) depicted the fast-running cycle of *Lepus californicus,* showing both the gathered and the extended suspension and filmed at 200 fps. Simons (1999) depicted the fast-running cycle of the domestic rabbit with both suspension stages filmed at 100 fps in X-ray to visualize viscera movements. Bertram and Gutmann (2009) depicted the slow-running cycle of *L. townsendii* with only one suspension stage. Like in Marey's faster rabbit, it appears after the forelimb thrust and, thus, corresponds to the gathered suspension. However, the forelimbs and hindlimbs are not really gathered under the body but remain parallel to each other like in a pronking (stotting) gait of gazelle or mara (Climaco das Chagas et al., 2019). Kuznetsov et al. (2017) published a video recording image sequence of a cornering maneuver of *L. europaeus* and also represented its gait diagram for maneuver and fast forward running. As to pikas, their half-bound gait was recorded due to successful keeping of

[1] https://www.youtube.com/watch?v=cqVlnVEcGwg

a population of *O. rufescens* in Germany and appeared in a series of papers on locomotion of small mammals, with *O. rufescens* as a central object (Witte et al., 2002; Hackert et al., 2006; Schilling and Hackert, 2006). Both suspension stages were brief, so for pictures of faster running pikas one must return to Gambaryan (1974).

Limb Architecture

Camp and Borell (1937) were the first to compare the hindlimb bones and muscles of lagomorphs using a series of increasingly cursorial taxa: *Ochotona*, *Sylvilagus*, and *Lepus*. They note a tendency in this series in which muscle bellies become shorter, and tendons become longer. The first research of the entire postcranial locomotor apparatus of Mongolian species of pikas, aimed at ecological interpretation, was a dissertation subject of Cevegmid (1950), but has never been published. Klebanova et al. (1971) presented a detailed account of postcranial bone dimensions and muscle masses and attachments for six pika and five leporid species. Lammers and German (2002) attempted to find the specific features in the growth of limb bones of the rabbit and chinchilla, both of which use a half-bound gait. Williams et al. (2007a) quantified the hindlimb muscles and tendons of *L. europaeus*. They did not cite the early paper by Camp and Borell (1937) but explained their finding of increased development of tendons in the hare's hindlimb as an adaption for elastic energy storage. The same authors (Williams et al., 2007b) published a similar analysis of the forelimb muscles of *L. europaeus*, showing that the tendons in the forelimb are less developed than in the hindlimb. This implies that the forelimbs have a smaller role in energy saving via elastic storage and recoil. Reese et al. (2013) compared limb bone proportions between the meadow-dwelling and talus-dwelling pikas and found differences that they qualitatively attributed to the different actions of digging in meadows versus leaping in rocks. Young et al. (2014) took the same series of increasing cursoriality represented by *Ochotona*, *Sylvilagus*, and *Lepus*, as was earlier studied by Camp and Borell (1937) and Fostowicz-Frelik (2007) and performed a morphometric analysis of fore- and hindlimb bones, examining relative length and robusticity. Their results suggest that with increasing cursoriality in lagomorphs, the proximal limb bones become more gracile (decrease in robustness), while the distal bones do not. They hypothesize that limb bone morphology of lagomorphs is indicative of a trade-off between locomotor economy (cursors requiring longer, gracile limbs) and the need to be fracture-resistant (i.e., more robust) in the distal regions involved in impact.

Locomotory Adaptations to Cornering

Although lagomorphs exhibit exceptional levels of maneuverability, there is only one scientific publication documenting this phenomenon (Kuznetsov et al., 2017). This study is based on field records of the *L. europaeus* chased by sighthounds. Hares' stereotyped turn begins by a lateral kick of a forelimb against the ground, which initiates the turn to the opposite side of the kicking forelimb. Centripetal forces are produced by the forelimbs, and the braking forces by the hindlimbs. In contrast, the chasing dogs perform braking by the forelimbs and therefore, sometimes somersault overhead.

The anterior and posterior halves of the hares' trunk yaw and roll separately. Separate rolling employs axial rotation in the thoracic region of the spine. The morphological application of this study is the explanation of unique hypertrophy of the musculus subclavius in lagomorphs with its expansion over the whole scapula. This muscle became a specialized pronator of the scapula (there is no other efficient pronator of the scapula in mammals). Contracting together with the musculus serratus ventralis cervicis, it ensures centripetal force production by the forelimb and, first, the lateral kick at the touch-down of the forelimb initiating the maneuver. In leporids, the musculus subclavius comprises 1% of the total muscular mass of the limbs, while in rodents no more than 0.5% (Gambaryan, 1974). In pikas, it comprises 4% of the total muscular mass of the limbs. The musculus serratus ventralis cervicis, which assists the musculus subclavius in the lateral kick, comprises 1.5% of the total muscular mass of the limbs in leporids, and 2.3% in pikas. The greater relative mass of both muscles in pikas may highlight their elevated ability for sharp turning and smaller prevalence of the hindlimbs.

Locomotory Adaptations of the Spine

In the leporid vertebral skeleton, the most prominent structures related to the unique role of axial bending during the half-bound are the ventral spinous processes of the three anterior lumbar vertebrae and the posterior two or three thoracic vertebrae (Klebanova et al., 1971; Gambaryan, 1974). These processes provide an additional attachment site for the major lumbar flexors, which comprise 5–10% of the total muscular mass of the limbs in lagomorphs but never more than 5% in ungulates and carnivorans (Gambaryan, 1974). The antagonists extending the spine are equivalent to 30% of the total muscular mass of the limbs in leporids and 15% in pikas. In addition to the unique ventral spinous processes, leporids also show a set of skeletal features typical to other dorsomobile mammals. These are the elongate and anteriorly inclined transverse processes and short and anteriorly inclined dorsal spinous processes of lumbar vertebrae (Gambaryan, 1974; Jones et al., 2018).

Vertebral range of motion was studied *in vitro* in three lumbar joints (those between vertebrae L4–L7) of the rabbit (Grauer et al., 2000). It was found that each lumbar joint can be flexed ventrally by 12–15°, extended dorsally by 6°, bent laterally by 4–8°, and rotated axially to every side by about 1°. The prevalence of sagittal flexion and extension, as well as reduction of axial twisting of the lumbar region is expected given what is known about overall locomotor behavior in lagomorphs. *In vivo* spine movements in the sagittal plane were studied for pikas based on high-frequency filming in X-ray (Schilling and Hackert, 2006). Simons (1999) filmed rabbit running to study a visceral piston hypothesis according to which the breath in gallop is synchronized with the stages of locomotor cycle and with spine sagittal bending. The inertia of the viscera, and especially of the liver, are said to act as a pump for inhalation and exhalation, while the activity of the diaphragm and rib cage muscles might be virtually unnecessary. Simons (1999) falsified this hypothesis for the rabbit by showing inappropriate mutual phasing of locomotor

and breathing cycles. Instead, an idea of pneumatic stabilization of the thorax was suggested.

Cranial Kinesis and Locomotion

Cranial kinesis is the ability of bones of the cranium to move relative to each other (as such, it is opposed to the mobility of visceral skeleton, e.g., jaw opening and movements of the middle ear ossicles). Cranial kinesis within leporids, unknown among other mammals, has been suggested to play an important role in locomotor behavior (Bramble, 1989), though the extent of this kinesis of leporid has not yet been fully characterized. In both ochotonids and leporids, ethmoid-orbital and otic-occipital part parts of the braincase are partially separated laterally by a piriform fenestra that passes subvertically along the posterior border of os alisphenoideum and (in leporids) os squamosum (Wible, 2007). Ventrally, the piriform fenestra comes into a transverse fissure which separates os basisphenoideum from os basioccipitale (in contrast to tight junction or even fusion of those two bones in other mammals). Notably, this is not a fetal, but an adult condition. Thus, the piriform fenestra and basisphenoid/basioccipital fissure serve as an intracranial joint, which Bramble (1989) suggests helps to dampen forces that occur during the locomotor cycle of lagomorphs, especially in high-speed hares. Due to soft tissue attachments across the intracranial joint, the large ears of hares may also act to support and reset the anterior (ethmoid-orbital) part of the cranium (Stott et al., 2010).

Bramble (1989) assumed that in steady quadrupedal running the forelimbs produce a significant braking effect, while the hindlimbs primarily accelerate the body. In fact, this was a common assumption at that time, which was shared by Gambaryan (1974) in his biomechanical considerations of a wide variety of mammals. More recent force-plate recordings, including those for pikas (Witte et al., 2002), show two significant patterns that challenge earlier assumptions. First, the vertical component of the ground reaction force in steady terrestrial walking and running is always several times greater than the horizontal component (longitudinal and transversal). Second, the longitudinal horizontal component is directed posteriorly (braking the body) in the first half of the contact phase, and anteriorly (accelerating the body) in the second half. This is true for both for the forelimb and the hindlimb. Therefore, the rule is not the deceleration by the forelimb and acceleration by the hindlimb, but deceleration in the first part of the contact phase of every limb and acceleration in the second part. It is also of note that large horizontal forces and accelerations take place not in steady running but at the rapid start and stop of the forward motion and in cornering. At the start and stop, longitudinal forces prevail, while in cornering the transverse forces are dominant. Thus, during cornering, the anterior part of the skull may tend to yaw centrifugally. In fact, Bramble (1989) has described the structure that prevents this distortion of the head, although he did not appreciate its adaptive role. In leporids, the os squamosum has a specific process, "the petrosal bar" which protrudes far posteriorly, crosses the piriform fenestra, and is housed by a matching "supratympanic sulcus" in the os petrosum. Therefore, the left and the right petrosal bars brace the basicranial block of the skull from both sides preventing lateral distortions in
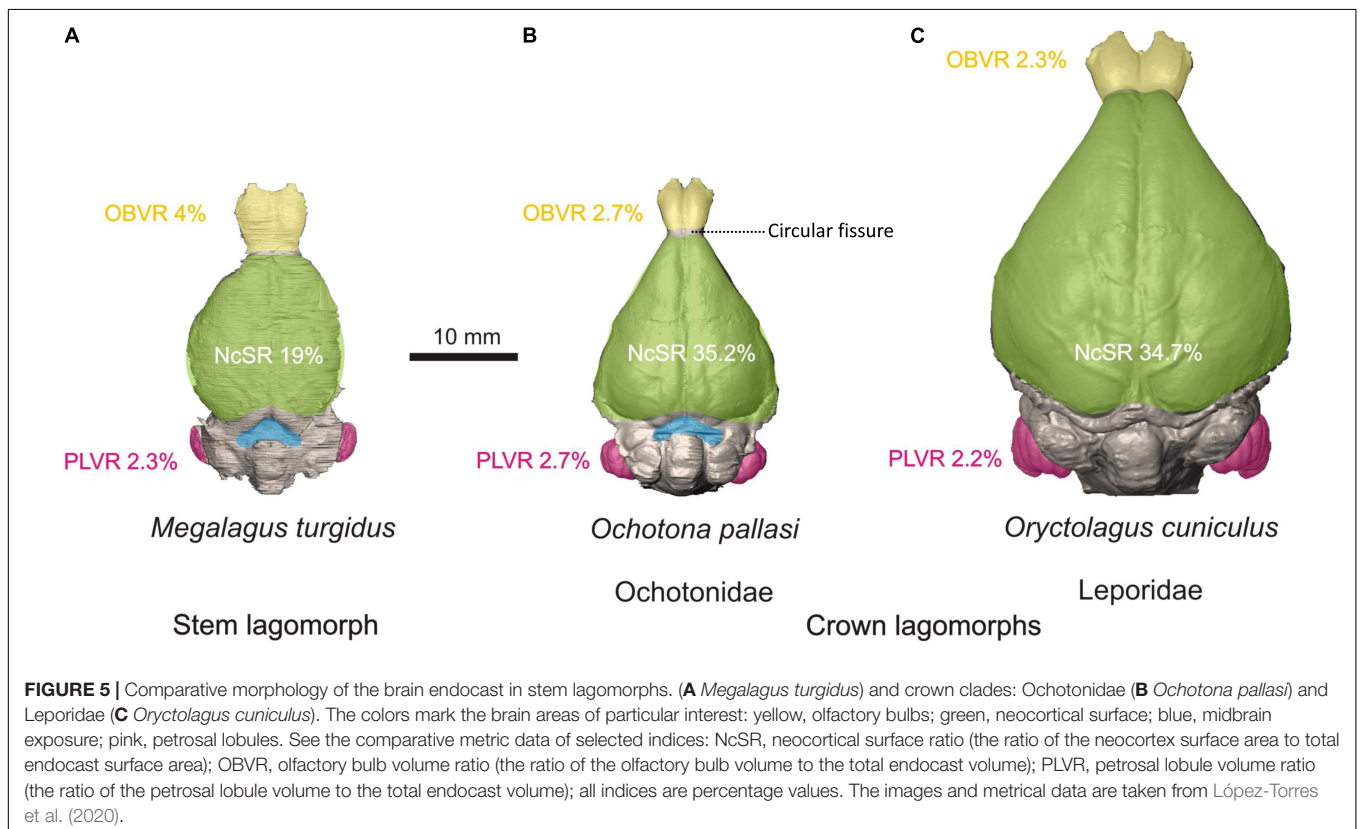
the kinetic zone in case of transverse accelerations. In such cases the heavy ears fall aside (Kuznetsov et al., 2017) and cannot help to save skull integrity.

BRAIN EVOLUTION

Rabbits are well-known laboratory mammals for which there is an extensive historical record of the study of their brain morphology starting in the late 19th century (see Lewis, 1882; Mann, 1895; and references therein). Although the brain of the domesticated rabbit (*O. cuniculus*) is well studied, little is known about the evolution of the lagomorph brain. Until recently, data on brain morphology of fossil lagomorphs were derived from the fossil natural endocasts of *Prolagus* (Edinger, 1929), *Hypolagus* (Sych, 1967; Czyżewska, 1985), and *Palaeolagus* (Cope, 1884, but see Wood, 1940). These show similarities with modern lagomorph brains, such as narrow frontal lobes. The growing accessibility of µCT data has transformed the way we understand endocranial anatomy, especially regarding incorporation of quantitative data. The first virtual endocast of a fossil lagomorph, *Megalagus turgidus*, was described by López-Torres et al. (2020). The cranium of *M. turgidus* is the oldest (early Oligocene; Olson, 1942) and most complete lagomorph cranium for which mostly complete endocranial information can be recovered. Historically, *M. turgidus* has been classified as a leporid (Olson, 1942; Dawson, 1958, 2008), but more recently it has been considered to belong to a more primitive lineage

outside crown lagomorphs (Lopez-Martinez, 2008). In the most comprehensive relevant phylogenetic analyses, the position of *Megalagus* as a stem lagomorph was supported (Fostowicz-Frelik, 2013; Fostowicz-Frelik and Meng, 2013). The study of the endocast of a stem lagomorph provides us with very valuable information on the brain morphology of lagomorphs before the split between the leporid and ochotonid lineages.

The endocast of *Megalagus turgidus* (**Figure 5A**) shows it had larger olfactory bulbs relative to its endocranial volume than any modern lagomorph. With respect to the cerebrum, the frontal lobes of *Megalagus* are wider than those observed in modern lagomorphs (narrow frontal lobes are a typical modern lagomorph trait), but they also are not as expanded rostrally, exposing much of the circular fissure. In contrast, ochotonids generally exhibit exposure of a portion of the circular fissure, and the circular fissure is covered in leporids (**Figure 5B**). The endocast of *Megalagus* possesses only a lateral sulcus on the neocortex, similar to the condition seen in leporids. The cerebral outline in dorsal view is markedly different among *Megalagus*, modern leporids, and modern ochotonids. The broadest point in the cerebrum of *Megalagus* is approximately midway between the rostral and caudal ends of the cerebrum, making the endocast have a rather ovoid outline. In contrast, leporids and ochotonids both have cerebra that are much broader in their caudal region (**Figure 5**). Therefore, there was likely a shift in lagomorph evolution to expand the caudal area of the cerebrum through time. In the caudal end of the cerebrum, the midbrain is partially exposed in *Megalagus*, similar to midbrain exposure in other

FIGURE 5 | Comparative morphology of the brain endocast in stem lagomorphs. (**A** *Megalagus turgidus*) and crown clades: Ochotonidae (**B** *Ochotona pallasi*) and Leporidae (**C** *Oryctolagus cuniculus*). The colors mark the brain areas of particular interest: yellow, olfactory bulbs; green, neocortical surface; blue, midbrain exposure; pink, petrosal lobules. See the comparative metric data of selected indices: NcSR, neocortical surface ratio (the ratio of the neocortex surface area to total endocast surface area); OBVR, olfactory bulb volume ratio (the ratio of the olfactory bulb volume to the total endocast volume); PLVR, petrosal lobule volume ratio (the ratio of the petrosal lobule volume to the total endocast volume); all indices are percentage values. The images and metrical data are taken from López-Torres et al. (2020).

primitive Euarchontoglires (e.g., most plesiadapiforms; Silcox et al., 2009, 2010; Orliac et al., 2014).

With respect to the modern lagomorph lineages, the range of relative olfactory bulb size of ochotonids is found within the range of leporids (López-Torres et al., 2020). In modern leporids, the midbrain is completely covered, and in modern ochotonids the midbrain is only slightly exposed (**Figure 5C**). The endocasts of ochotonids are completely lissencephalic, contrary to the endocasts of leporids, which only possess a lateral sulcus on the neocortex. The main difference in the cerebral outline between leporids and ochotonids is that the antero-lateral margins of the cerebrum in dorsal view are concave in leporids and either straight or slightly convex in ochotonids. This makes leporids have a rather pear-shaped dorsal outline, whereas in ochotonids it is more triangular (**Figure 5**). Modern lagomorph lineages also differ in that leporids have a proportionally longer (and larger) cerebrum than ochotonids (López-Torres et al., 2020).

Some tentative conclusions can be sketched about trends in the evolution of the lagomorph brain. Leporid and ochotonid lineages differ in many aspects of brain morphology, including the rostral expansion of the frontal lobes in leporids, a higher relative petrosal lobule volume in ochotonids, and the caudal expansion of the occipital region of the cerebrum in leporids. With respect to the latter, Kraatz et al. (2015) and Kraatz and Sherratt (2016) suggested a need for increased visual perception of the substrate in leporids, which might explain the more developed caudal region of the cerebrum in that group. In contrast, *Megalagus* exhibits a more 'primitive' brain, sharing more resemblances to endocasts that have been reconstructed for early fossil rodents (i.e., ischyromyids; Bertrand and Silcox, 2016; Bertrand et al., 2016, 2019) and plesiadapiforms (Silcox et al., 2009, 2010; Orliac et al., 2014). In particular, *Megalagus* has fairly large, pedunculated olfactory bulbs, some extent of midbrain exposure, and low neocorticalization. As in larger plesiadapiforms and rodents, *Megalagus* develops a lateral sulcus, with the brain being otherwise lissencephalic. These similarities with primitive members of Euarchontoglires, such as plesiadapiforms and primitive rodents, may indicate that lagomorphs are an old, relatively basal lineage and that they are conservative in their morphology.

LAGOMORPHS AS BIOMECHANICAL MODELS

Rabbits were one of the first vertebrates for which the *in vivo* range of sarcomere shortening was precisely measured with diffraction techniques (Dimery, 1985). Contrary to the previous expectations, the shortening range in 12 hindlimb muscles appeared to be much less than 30%. The shortening employs the plateau of the well-known force-tension curve, which is the best for force production. Until now, similar data are available for very few other vertebrate species other than humans and rabbits (Burkholder and Lieber, 2001). Additionally, it has been shown that the number of successive sarcomeres in myofibrils directly depends on the excursions experienced by the muscle during

an individual's growth. Koh and Herzog (1998) released the musculus tibialis anterior from its retinacular restraint in 4-week-old rabbits. Free of the restraint, the muscle gained increased range for shortening and extension with the unchanged angular amplitude in the ankle joint. Twelve weeks later the operated muscles showed considerable difference from the control; muscle fibers became longer, while the tendons became shorter. As a byproduct, the force of operated muscle decreased. Rabbits have also proven to be a convenient model animal for human orthopedics. They are used in biomechanical modeling of the joints of both the spine (Grauer et al., 2000) and the limbs (Grover et al., 2007).

Cranial Biomechanics

Beyond those detailed by Bramble (1989), other morphological features of the cranium have been associated with locomotion including a pronounced ventral flexion of the facial region and unique fenestrations in the posterior cranial bones and lateral portion of the maxilla (DuBrul, 1950; Moss and Feliciano, 1977; Stott et al., 2010; Kraatz et al., 2015; Kraatz and Sherratt, 2016). The unique rostral vacuity (Ochotonidae) and fenestration (Leporidae) in lagomorphs were noted by Gray (1867), and DuBrul (1950) suggested that the latticing of the maxilla in Leporidae could increase the efficiency of speedy locomotion by reducing weight of the rostrum, and potentially contributing to Bramble's (1989) anterior capital suspensory system hypothesis. However, Moss and Feliciano (1977) argued that these fenestrations are related to the lack of transmission of masticatory forces through the lateral aspect of the rostrum. They proposed that the more vertical orientation of the ramus of the mandible in some leporids redirects incisal forces along the dorsal and ventral aspects of the rostrum, and away from the lateral side. Although this has yet to be tested, methods such as *in vivo* strain-gage analysis coupled with *in silico* finite element analysis could provide more resolution.

Leporids process food through differing modes of mastication within a single bite cycle (Weijs, 1980), including incisor biting, molar crushing and molar shearing, and the potential influence of these modes on bone deposition and skull shape, including the fenestrated rostrum, remains unknown. Biomechanical modeling using multibody dynamics analysis has demonstrated varied muscle lines of action and bite force magnitudes and directions during a bite cycle (Watson et al., 2014). However, it is unknown whether the largest and/or more frequent masticatory strains across the whole cranium are generated through incisor biting, and how these are directed through the rostrum, or by crushing or shearing of food at the molars. What is evident is that the bony form of the circumorbital region, cranial vault and basicranium in lagomorphs is unlikely to be related to stresses experienced during biting and chewing (Jašarević et al., 2010; Franks et al., 2016, 2017). The debate about determinants of skull form, however, continues, as faster, saltatorial species such as hares and jackrabbits of the genus *Lepus*, have more extensive fenestration and a more pronounced ventral facial tilt (Kraatz et al., 2015; Kraatz and Sherratt, 2016). This is in comparison to generalists, including cottontail and pygmy rabbits (e.g., *Sylvilagus* spp. and *B. idahoensis*), suggesting that there

may be a correlation between posture, locomotion, and rostral fenestrations as well as mastication.

Feeding Apparatus

In many ways, the function of the lagomorph oral cavity is especially well known among mammals. This is due largely to *in vivo* studies of jaw-adductor muscle activity, jaw kinematics and mandibular bone strain, and more recent work on diet-induced adaptive plasticity in domestic white rabbits (*O. cuniculus*). Rabbits exhibit a vertically deep facial skull and a jaw joint correspondingly elevated above the toothrow that that allows the jaw both rotational and translational movements (Weijs and Dantuma, 1981; Crompton et al., 2006). Transverse mandibular movements during the chewing cycle in rabbits are similar to primates in being due to delayed activity of the balancing-side deep-masseter muscle, which is in part related to dietary stiffness, i.e., elastic modulus (Weijs and Dantuma, 1981; Hylander et al., 1987, 2000; Weijs et al., 1989; Agrawal et al., 1997, 1998, 2000; Vinyard et al., 2006). Such kinematics are facilitated via a partially fused mandibular symphysis, a midline anteriorly located joint that closely binds the two jaw halves (Weijs and Dantuma, 1981; Ravosa and Hogue, 2004; Ravosa et al., 2016). Rabbits and diverse mammals have similar mandibular peak strains during the mastication of mechanically challenging foods (Weijs and de Jongh, 1977; Ravosa et al., 2010b). Rabbits share feeding patterns with other mammals whereby items with greater toughness and/or higher stiffness require larger and protracted jaw-adductor forces during biting and chewing, which results in greater occlusal forces and masticatory stresses (e.g., Herring and Scapino, 1973; Weijs and de Jongh, 1977; Hylander, 1979; Gorniak and Gans, 1980; Weijs and Dantuma, 1981; Dessem and Druzinsky, 1992; Hylander et al., 1992, 1998, 2000; Ravosa and Hogue, 2004; Vinyard et al., 2008). Rabbits are likewise noteworthy due to extensive ontogenetic data about the *in vivo* links among masticatory function, feeding behavior and food mechanical properties (e.g., Weijs et al., 1987, 1989; Langenbach et al., 1991, 2001; Langenbach and van Eijden, 2001; Martin et al., 2020).

Skeletal adaptations are related to either high-magnitude, singular loads or low-magnitude, cyclical loading. Although high bite forces have long been linked to greater jaw robusticity in mammals (e.g., Hylander, 1979), the dietary underpinnings of repetitive or cyclical loading are still poorly known for masticatory features. Rabbits are but one of two taxa for which mechanically challenging foods are known elevate cyclical loading (Ravosa et al., 2015; Nett et al., in press). Rabbits also resemble mid-to-large sized mammals in exhibiting intracortical remodeling, a skeletal repair mechanism related to microcrack damage in adult bone that does not appear to characterize smaller species (Bouvier and Hylander, 1996a,b; Hirano et al., 2000; Lad et al., 2021).

Rabbits are perhaps the best studied mammals in terms of dietary plasticity in the skull and jaws. A series of experiments have explored the implications of dynamic changes in elevated and cyclical loads on craniomandibular ontogeny and function in rabbits subjected to long-term, naturalistic modifications of dietary properties (Ravosa et al., 2007, 2016). Analyses have explored ontogenetic variation in jaw-loading patterns due to seasonality and fallback foods (Scott et al., 2014a,b); differences in age-related performance of bone and cartilage in jaw joints (Ravosa et al., 2007, 2008; Jašarević et al., 2010; Ravosa and Kane, 2017); reaction norms of bony vs. muscular components (Ravosa et al., 2010a); regional and hierarchical variation in patterns of cranial bone formation (Ravosa et al., 2007; Menegaz et al., 2009; Franks et al., 2016, 2017; Terhune et al., 2020; Lad et al., 2021); and morphological inference in the fossil record (Ravosa et al., 2016). Another finding is that dietary plasticity in rabbit jaws is similar to shorter-term studies of this phenomenon in monkeys, hyraxes, ferrets and rats (Beecher and Corruccini, 1981; Bouvier and Hylander, 1981, 1996a,b; Beecher et al., 1983; Yamada and Kimmel, 1991; He and Kiliaridis, 2003; Lieberman et al., 2004). These integrative analyses have marshaled a suite of histological, imaging and engineering approaches to understand masticatory development and phenotypic diversity in rabbits. Despite the differential focus of such research on the role of long-term plasticity in craniomandibular evolution and diversity, such an ontogenetic perspective to the mechanobiology of lagomorphs invariably lends itself to ongoing revolutions in 'omics' as well as clinical approaches to aging and pathobiology of connective tissues.

CLINICAL MODEL

Understanding of the healthy rabbit masticatory system and cranial morphology is important for diagnosis and treatment of dental disease in rabbits (Harcourt-Brown, 2007; Lennox, 2008; Jekl and Redrobe, 2013). The rabbit is also one of the most used animals in clinical experimental modeling (Neyt et al., 1998; Stübinger and Dard, 2013), often used to investigate the remodeling of bone in response to dental implants (Kim and Shin, 2018; Leventis et al., 2018; Manju et al., 2018) and impaired muscle function (Balanta-Melo et al., 2019; Huang et al., 2019). Rabbits are also a good clinical model for craniosynostosis, a condition that involves the premature closure of cranial sutures in infants. Craniosynostotic rabbits are the only existing colony of any species affected by familial craniosynostosis in the world (Mooney et al., 1998a,b; Cooper et al., 1999; Lyn Chong et al., 2003). Suture defects must be artificially created to investigate this question in any other species of mammal. Therefore, these rabbits are the most similar non-human model to naturally occurring craniosynostosis in other mammals and require less surgical manipulation.

SUMMARY

Though model organisms are critical tools for understanding much of the biology of life, larger systems of organisms can offer a more dynamic and comparative framework to reveal the tempo and mode of evolutionary change. Understanding the adaptive processes that drive these changes is often best accomplished by studying groups of closely related organisms at multiple time scales. We offer the Lagomorpha

(rabbits, hares, pikas, and their ancestors) as an exemplar system in which to study the evolutionary patterns of morphologic change. Anchored by the common laboratory rabbit (*O. cuniculus*), the order offers a rich diversity of extant species within the monogeneric Ochotonidae and the more lineage rich Leporidae. The molecular phylogenetics of these groups have been well studied, and indeed, four species have established genome level architecture. Understanding lagomorph intraordinal relationships has also advanced through a rich, consistent fossil record that dates back nearly 50 million years. The evolutionary trees are already in place to develop phylogenetically constrained models of evolution, but more work is needed combining molecular and morphological data into a comprehensive phylogeny of lagomorphs.

Using existing phylogenetic frameworks and emerging methods, lagomorphs are already an excellent system in which to study a rich array of functional systems. The locomotor behavior of these small mammals has been of long-standing interest, and research within this system has increasingly incorporated evidence from the fossil record, soft tissue systems, and novel connections to the cranium. The expanding research on the lagomorph cranium has shown important patterns of evolution of the brain and auditory systems and new methods have only increased the scope and breadth of research on the lagomorph masticatory system. The European rabbit will continue to remain a seminal research species for the biological sciences. Most importantly, new methods have allowed researchers to expand our knowledge more broadly among rabbit relatives, offering a more explicitly evolutionary context. The emergence of new methods of morphological research, an ever-improving phylogenetic framework, and a growing interest in lagomorphs will only serve to better place rabbits and *all* of their relatives as an essential system in which we can better understand the patterns and processes of evolutionary morphology.

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