Evolution of the patellar sesamoid bone in mammals

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The patella is a sesamoid bone located in the major extensor tendon of the knee joint, in the hindlimb of many tetrapods. Although numerous aspects of knee morphology are ancient and conserved among most tetrapods, the evolutionary occurrence of an ossified patella is highly variable. Among extant (crown clade) groups it is found in most birds, most lizards, the monotreme mammals and almost all placental mammals, but it is absent in most marsupial mammals as well as many reptiles. Here we integrate data from the literature and first-hand studies of fossil and recent skeletal remains to reconstruct the evolution of the mammalian patella. We infer that bony patellae most likely evolved between four to six times in crown group Mammalia: in monotremes, in the extinct multituberculates, in one or more stem-mammal genera outside of therian or eutherian mammals, and up to three times in therian mammals. Furthermore, an ossified patella was lost several times in mammals, not including those with absent hindlimbs: once or more in marsupials (with some re-acquisition), and at least once in bats. Our inferences about patellar evolution in mammals are reciprocally informed by the existence of several human genetic conditions in which the patella is either absent or severely reduced. Clearly, development of the patella is under close genomic control, although its responsiveness to its mechanical environment is also important (and perhaps variable among taxa). Where a bony patella is present it plays an important role in hindlimb function; especially in resisting gravity by providing an enhanced lever system for the knee joint. Yet the evolutionary origins, persistence and modifications of a patella in diverse groups with widely varying habits and habitats -- from digging to running to aquatic, small or large body sizes, bipeds or quadrupeds -- remain complex and perplexing, impeding a conclusive synthesis of form, function, development and genetics across mammalian evolution. This meta-analysis takes an initial step toward such a synthesis by collating available data and elucidating areas of promising future inquiry.

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8 Running head: Patellar evolution in mammals

9   **Abstract**

10   The patella is a sesamoid bone located in the major extensor tendon of the knee joint, in the
11   hindlimb of many tetrapods. Although numerous aspects of knee morphology are ancient and
12   conserved among most tetrapods, the evolutionary occurrence of an ossified patella is highly
13   variable. Among extant (crown clade) groups it is found in most birds, most lizards, the
14   monotreme mammals and almost all placental mammals, but it is absent in most marsupial
15   mammals as well as many reptiles. Here we integrate data from the literature and first-hand
16   studies of fossil and recent skeletal remains to reconstruct the evolution of the mammalian
17   patella. We infer that bony patellae most likely evolved between four to six times in crown group
18   Mammalia: in monotremes, in the extinct multituberculates, in one or more stem-mammal genera
19   outside of therian or eutherian mammals, and up to three times in therian mammals. Furthermore,
20   an ossified patella was lost several times in mammals, not including those with absent hindlimbs:
21   once or more in marsupials (with some re-acquisition), and at least once in bats. Our inferences
22   about patellar evolution in mammals are reciprocally informed by the existence of several human
23   genetic conditions in which the patella is either absent or severely reduced. Clearly, development
24   of the patella is under close genomic control, although its responsiveness to its mechanical
25   environment is also important (and perhaps variable among taxa). Where a bony patella is present
26   it plays an important role in hindlimb function; especially in resisting gravity by providing an
27   enhanced lever system for the knee joint. Yet the evolutionary origins, persistence and
28   modifications of a patella in diverse groups with widely varying habits and habitats -- from
29   digging to running to aquatic, small or large body sizes, bipeds or quadrupeds -- remain complex
30   and perplexing, impeding a conclusive synthesis of form, function, development and genetics
31   across mammalian evolution. This meta-analysis takes an initial step toward such a synthesis by
32   collating available data and elucidating areas of promising future inquiry.

33   INTRODUCTION

34   This meta-analysis addresses the evolution of the ossified patella (tibial sesamoid or "kneecap"
35   bone) in mammals. Our focus was on the evolutionary pattern of how bony patellae evolved in
36   the mammalian lineage, as evidence of osseous patellae is simplest to interpret. However, as
37   explained further below we also consider non-bony sesamoids to also be potential character states
38   of the patellar organ; vexing as the form, fossil record and ontogeny (and thus homology) of
39   those soft-tissue structures are. We compiled voluminous literature and firsthand observational
40   data on the presence or absence of the osseous patella in extinct and extant mammals, then
41   conducted phylogenetic analysis of patellar evolution by mapping these data onto a composite
42   phylogeny of mammals (Kielan-Jaworowska et al. 2004; Luo 2007a; Luo 2007b) using multiple
43   phylogenetic optimization methods. We used the results to address patterns of acquisition and
44   loss (i.e. gain and loss of ossification) of this structure within Mammaliaformes. In particular, we
45   investigated whether an ossified patella was ancestrally present in all crown group Mammalia,
46   and lost in particular groups especially marsupials (Metatheria), or whether it evolved multiple
47   times in separate crown clades. Furthermore, if the bony patella had multiple origins, how many
48   times was it gained or lost, and what did it become if it was lost (such as a vestigial fibrocartilage
49   versus complete loss, without any evidence of a sesamoid-like tissue within the patellar tendon)?
50   These were our study's key questions. We provide some broader context here first.

51   Some aspects of the morphology of the knee in tetrapods (four-legged vertebrates bearing limbs
52   with digits) are evolutionarily ancient. Tetrapods had their ancestry amongst lobe-finned
53   sarcopterygian fish, in which jointed, muscular fins transitioned into limbs. Early stages of
54   distinct bony articulations between the femur and tibia-fibula are evident in the hind fins/limbs of
55   Devonian (~370 million years ago; Mya) animals such as *Eusthenopteron*, *Panderichthys*, and
56   *Ichthyostega* (Ahlberg et al. 2005; Andrews & Westoll 1970; Boisvert 2005; Dye 1987; Dye
57   2003; Haines 1942). These fossil sarcopterygians also have subtle differences between the
58   homologous joints in the pectoral fin/forelimb and the pelvic fin/hindlimb, indicating that
59   specification of forelimb/hindlimb identity was already in place (Boisvert 2005; Daeschler et al.
60   2006; Shubin et al. 2006). Furthermore, the morphology of the forelimb and hindlimb joints
61   indicates divergent functions of these limbs, with the forelimb evolving into a more
62   "terrestrialized" capacity earlier than the hindlimb (Pierce et al. 2012). Developmental and
63   morphological modifications to the hindlimb and particularly the mid-limb joint between the
64   stylopod and zeugopod continued, until a recognizable knee articulation of almost modern,
65   derived aspect arose in tetrapods of the Carboniferous period, ~350 Mya (Dye 2003).

66   Sesamoids are best defined as "skeletal elements that develop within a continuous band of regular
67   dense connective tissue (tendon or ligament) adjacent to an articulation or joint" (Vickaryous &
68   Olson 2007). The tibial patella is a sesamoid bone that arises during development within the main
69   extensor tendon of the knee, subsequently 'dividing' it (though there remains some continuity)
70   into the quadriceps and patellar tendons (the latter is sometimes inappropriately called the patellar
71   ligament) (Bland & Ashhurst 1997; Fox et al. 2012; Pearson & Davin 1921a; Tecklenburg et al.
72   2006; Tria & Alicea 1995; Vickaryous & Olson 2007). These tendons span from the quadriceps
73   muscle group to the tibia (Fig. 1). The patella itself tends to be incorporated mainly into the
74   vastus muscles of the quadriceps in mammals, with the tendon of M. rectus femoris lying more
75   superficial to them (Tria & Alicea 1995), with variable degrees of attachment to it (Jungers et al.
76   1980). Hereafter, the term "patella" implies ossification and hindlimb localization unless
77   otherwise specified (some literature inconsistently and confusingly refers to non-ossified
78   cartilaginous structures in this location as patellae—this homology in many cases needs better

79 testing), and implicitly refers to either a single patella or the left and right patellae normally
80 present in an individual. There is an "ulnar patella" in the forelimbs of some taxa (notably lizards,
81 but also some frogs, birds and mammals (Barnett & Lewis 1958; Haines 1940; Maisano 2002a;
82 Maisano 2002b; Pearson & Davin 1921a; Pearson & Davin 1921b; Romer 1976; Vanden Berge &
83 Storer 1995; Vickaryous & Olson 2007)) but a full discussion of this enigmatic structure is
84 beyond the scope of this study. Figure 2 depicts the anatomical orientations used throughout this
85 study to refer to tetrapod limbs.

86 The patella appears broadly similar amongst mammals possessing it, as far as has been studied,
87 although it varies greatly in size, generally in accordance with body size. It ossifies
88 endochondrally; from a cartilaginous precursor (i.e. anlage (Vickaryous & Olson 2007));
89 relatively late in gestation (e.g. sheep, goats (Harris 1937; Parmar et al. 2009)) or sometime after
90 birth (e.g. rabbits, rats, mice, humans (Bland & Ashhurst 1997; Clark & Stechschulte 1998;
91 Patton & Kaufman 1995; Spark & Dawson 1928; Tria & Alicea 1995; Walmsley 1940)). Very
92 recently, the development of the patella in mouse embryos was re-examined and the claim made
93 that the patella develops as a process that branches off the femur, strongly influenced by
94 mechanical loading in that region (Eyal et al. 2015). Whether this truly happens as described in
95 mice, let alone other mammals, and whether it can be accepted as unexpected support for the
96 "traction epiphysis" origin of patellar sesamoids (e.g. Pearson & Davin, 1921a,b), remains to be
97 determined, but the surprising results deserve attention. The general form of the osseous patella
98 in mammals is a hemispherical structure, with a superficial surface (covered by fibrocartilage
99 (Clark & Stechschulte 1998) and quadriceps tendon fibres (Bland & Ashhurst 1997)) and a deep
100 surface which articulates with the femur, gliding along the patellar sulcus or groove in that bone.
101 In maturity, the patella is composed of an outer lamellar cortex enclosing an inner cancellous
102 bone structure with marrow spaces, and has an articular hyaline cartilage lining on the deep
103 surface for articulation with the patellar sulcus (groove) of the femur (Benjamin et al. 2006; Clark
104 & Stechschulte 1998; Vickaryous & Olson 2007).

105 The vastus muscles' tendons (especially M. vastus intermedialis) may have a fibrocartilaginous
106 region at the approximate position of the patella, called the "suprapatella" or "patelloid" (Fig. 1).
107 The latter two terms are sometimes used synonymously, though "suprapatella" is more usual
108 when an osseous patella is also present, and "patelloid" when it is not. The suprapatella is
109 described as proximal to the patella, occasionally with a fat pad interposed between it and the
110 ossified patella (Fig. 1), whilst the patelloid is described as occupying the same approximate
111 region that a bony patella would (though absence of a patella makes this difficult to objectively
112 assess) (Bland & Ashhurst 1997; Jungers et al. 1980; Ralphs et al. 1991; Ralphs et al. 1998;
113 Ralphs et al. 1992; Reese et al. 2001; Walji & Fasana 1983). It is not clear whether the fibrous
114 patelloid in some marsupials (and perhaps some bats (Smith et al. 1995)) is homologous to the
115 suprapatella, equivalent to an evolutionarily reduced patella, or an independently occurring
116 structure. We revisit this problem later in this study.

117 The human patellar anlage is first visible at O'Rahilly stage 19, and chondrifies at stage 22.
118 Ossification begins 14 weeks after birth (Merida-Velasco et al. 1997a; Merida-Velasco et al.
119 1997b; Tria & Alicea 1995), but is not grossly visible until 4-6 years of age (when multiple,
120 eventually-coalescing centres of ossification can be seen radiographically (Ogden 1984)) and
121 sometimes not in its fully ossified form until adolescence. The patella is the only sesamoid bone
122 counted regularly among the major bones of the human body (Vickaryous & Olson 2007),
123 although there are other, much smaller sesamoids in the hands and feet (and in some cases even
124 the spine (Scapinelli 1963)). The pisiform is often considered a sesamoid and deserves further

125   attention in a broad context similar to this study's. Other small sesamoids, such as the lunula,
126   fabella, cyamella and parafibula, also occur in the knee joint in many tetrapod species including
127   some mammals (Fig. 1); these occur sporadically in humans (Pearson & Davin 1921a; Sarin et al.
128   1999).

129   The patella is covered by the thickest layer of articular cartilage in the human body (Palastanga et
130   al. 2006). The patella may thus also play a protective role for the underlying joint architecture
131   (Haines 1974), in addition to protecting the patellar tendon from excessive compressive stresses
132   (Giori et al. 1993; Sarin & Carter 2000a; Wren et al. 2000). The patellar tendon itself, to the
133   extent that its properties are known for some species (e.g. humans), is stiff and strong, able to
134   withstand about twice as much stress as typical knee joint ligaments and enduring strains (i.e.
135   lengthening) of up to 11-14% (Butler et al. 1986). Regional variations in the microscopic
136   anatomy of the human patella have also been recognised, for example in tissue thickness and
137   nerve arrangement, which may reflect load distribution (Barton et al. 2007; Eckstein et al. 1992;
138   Toumi et al. 2006; Toumi et al. 2012). There is convincing evidence from numerous species that
139   excessive loads on the patella can lead to degeneration of the articular cartilages and damage to
140   the underlying bone, producing osteoarthritis (Aglietti & Menchetti 1995; Hargrave-Thomas et
141   al. 2013; Tria & Alicea 1995), so those regional variations of patellar structure are likely
142   important. Similarly, the tissues involved in anchoring the patellar tendon to the proximal and
143   distal surfaces of the patella as well as to the proximal tibia (tuberosity/tubercle) vary in their
144   composition and presumably are adapted, and exhibit phenotypic plasticity, to reduce the risk of
145   tendon avulsion from the bone (Evans et al. 1991). Reduction of a bony patella to soft tissue
146   presumably reduces its ability to act as a gear or lever (Alexander & Dimery 1985).

147   Functions of the patella notwithstanding, there was once some enthusiasm for its outright
148   removal for treatment of certain joint problems. Patellectomy was first performed in 1860 and for
149   some time was an established treatment option for several conditions (Pailthorpe et al. 1991;
150   Sweetnam 1964). However, partial and complete patellectomies are now considered as last resort
151   salvage procedures; this is also the mainstream view of the veterinary profession (Langley-Hobbs
152   2009). The historical lack of clarity on the pros and cons of patellectomy was summarised
153   eloquently by *The Lancet,* stating, "Sadly, most of our interventions on the patella are empirical,
154   and are supported more by the enthusiasm of proponents than by a very deep knowledge of the
155   biology or biomechanics of this unusual joint. The knee cap could do with more scientific
156   attention" (Editors 1992).

157   The latter complaint regarding the dearth of scientific attention to form, development, function
158   and clinical treatment of the patella applies even more so to non-human tetrapods. One exception
159   is a study that measured the inter- and intra-specific variability of the patellae and other bones
160   (Raymond & Prothero 2012). The latter study found generally greater variation in patellae (and
161   other sesamoids) vs. "normal" long bones. The inference was that this greater variability might
162   pertain to the "intermembranous" [*sic*- intramembranous] development of sesamoids, vs. an
163   endochondral location in long bones. However, the patella and most other major limb sesamoids
164   of mammals are pre-formed in cartilage and thus clearly are endochondral bones (Farnum 2007).
165   Yet the latter study reinforces that sesamoids are more variable than most other bones, in part due
166   to their mechanical environment, in part due to their embedding in soft tissues (themselves quite
167   variable) such as tendons and ligaments (Bland & Ashhurst 1997; Clark & Stechschulte 1998)
168   and perhaps due to other factors not yet understood. This uncertainty about the causes of
169   variability in the patella may also relate to incomplete understanding of its mechanical loading
170   and function *in vivo*, as follows.

171   Where a patella is present in its typical form, its primary function is to modify the mechanical
172   advantage (ratio of output force to muscle force) at the knee joint, by increasing the moment arm
173   of the tendon in which it is embedded and thereby altering the amount of force needed from the
174   quadriceps muscles in order to generate a particular moment (torque; rotational force) about the
175   knee joint (Alexander & Dimery 1985; Fox et al. 2012; Haines 1974; Heegaard et al. 1995;
176   Herzmark 1938; Howale & Patel 2013; Tecklenburg et al. 2006). In humans, the patella causes
177   the quadriceps muscle group's moment arm about the knee to increase as the knee becomes more
178   extended, causing the amount of quadriceps muscle force required per unit of patellar tendon
179   force (i.e. at the insertion onto the tibial tubercle) to vary significantly across knee joint flexion-
180   extension (Aglietti & Menchetti 1995; Fellows et al. 2005). By articulating with the femur, the
181   patella also transmits some forces of the quadriceps muscle group directly onto the femur (the
182   patellofemoral joint reaction force); forces which can reach a maximum of 20-25 times body
183   weight (Aglietti & Menchetti 1995).

184   The mobility of the patella is an important aspect of its function. While, in humans, the patella
185   mostly flexes and extends relative to the femur as the knee is flexed and extended, it also
186   translates and pitches (tilts) and rolls (Aglietti & Menchetti 1995; Fellows et al. 2005), leading to
187   variable contact between the patella and femur that is reflected in the angled facets of the human
188   patella (Lovejoy 2007). In contrast to the situation in humans (as well as in early hominins such
189   as *Australopithecus*), in chimpanzees and presumably many other primates (as well as other taxa
190   such as sheep (Bertollo et al. 2012; Bertollo et al. 2013)), the patella remains in tight articulation
191   with the femur throughout the knee's range of motion, reducing patellofemoral stresses especially
192   when the knee is strongly flexed, as it habitually is in those non-human primates (Lovejoy 2007).
193   Other primates show varying degrees of specialization of patellar morphology that alter the
194   moment arm of the patellar tendon, with great apes apparently having a patella most specialized
195   for widely varying knee joint postures (Pina et al. 2014). It has been claimed that in hominids and
196   ursids (bears) alike, there is an association between plantigrady (flat-footedness), increased knee
197   range of motion, and patellar mechanics (Lovejoy 2007); that is an interesting hypothesis that
198   could be rigorously tested.

199   In the elbow of humans and other mammals, there is an extension of the ulna called the olecranon
200   (process), which serves a lever-like function analogous to that of the patella (Herzmark 1938).
201   However, a mobile sesamoid bone like the patella has a more flexible ("dynamic gearing")
202   function in improving mechanical advantage compared with an immobile retroarticular process
203   like the olecranon (Alexander & Dimery 1985). There tends to be an inverse relationship between
204   mechanical advantage and speed of joint motion (Hildebrand 1998), thus a high mechanical
205   advantage is not necessarily useful in all cases, which may in part explain the variable
206   occurrence, size and shape of the patella in animals with different lifestyles and modes of
207   locomotion. Biomechanical studies of primates (Lovejoy 2007; Pina et al. 2014) and
208   domesticated mammalian species (e.g. dogs (Griffith et al. 2007; Kaiser et al. 2001), sheep
209   (Bertollo et al. 2012; Bertollo et al. 2013), horses (Schuurman et al. 2003; Wentink 1978)) have
210   contributed some knowledge of how the patella functions in these groups, or in individual
211   species, but a general "functional synthesis" for the patella is still lacking.

212   De Vriese performed pioneering comparative analyses and attempted syntheses of patellar size
213   and morphology in comparison to other leg bones, between species and among multiple
214   individuals in some species (De Vriese 1909). No clear correlations were observed between the
215   size of the patella and other major hindlimb bones (femur, tibia, and fibula). A correlation was

216 claimed between the sizes of the patella and the talus (or intermedium) in the ankle, although no
217 clear, plausible mechanistic/functional justification was suggested and no statistical analyses
218 were performed. Somewhat oddly, no relationship was evident between the size and shape of the
219 patella and the femoral patellar groove (De Vriese 1909). The more restricted but quantitative
220 analysis of Valois (Valois 1917) focused mainly on primates and challenged many of De Vriese's
221 claims that mechanical or physiological explanations of patellar morphology have "no scientific
222 merit". Haxton (1944) also criticised De Vriese for focusing on relative length of bones; his own
223 "patellar index" based on relative width found no correlation with animal speed or size, but he
224 inferred that the patella confers functional advantages in knee extension. There has been little
225 examination of these questions in a modern comparative, rigorously statistical or biomechanical
226 context since these studies. A notable exception is a study of the distal femur and patellar groove
227 in bovid mammals, indicating increased mechanical advantage of the knee in larger species
228 (Kappelman 1988).

229 The occurrence of an ossified patella in the knee joint is not universal among tetrapods (Fig. 3). A
230 bony patella is absent in extinct early Tetrapoda and crown clade Lissamphibia (Dye 1987;
231 Haines 1942; Herzmark 1938; Vickaryous & Olson 2007), all non-avian dinosaurs, Crocodylia,
232 and Testudines (turtles), and all other extinct tetrapods. Hebling et al. (2014; their fig. 3A)
233 illustrate what seems to be a patella formed of soft tissue in the bullfrog *Lithobates catesbeianus*.
234 That fascinating observation needs a more comprehensive examination across Anura and Urodela
235 to test if a soft tissue "patelloid" is ancestral for Lissamphibia or smaller clades. In contrast, an
236 ossified patella is present in many or most Squamata (lizards and kin) with limbs (Camp 1923;
237 Carrano 2000; De Vriese 1909; Dye 1987; Dye 2003; Gauthier et al. 2012; Haines 1940; Haines
238 1942; Hutchinson 2002; Hutchinson 2004; Jerez & Tarazona 2009; Maisano 2002a; Regnault et
239 al. 2016; Vickaryous & Olson 2007). Patellar status (used throughout our study to refer to
240 presence/absence of ossification in adults) is unknown for the (mostly extinct) Rhynchocephalia
241 (sister group to Squamata), although a patella is at least sometimes present in the tuatara
242 *Sphenodon* – the only extant rhynchocephalian (Regnault et al. 2016). An apparent sesamoid
243 bone was noted in the knee joint region of a specimen of *Macrocnemus*, a mid-Triassic (~235
244 Mya) reptile, which may be the earliest identified occurrence of a patella in any animal group
245 (Rieppel 1989), although this structure may have been a different sesamoid bone or ossicle. There
246 have been anecdotal accounts of fibrocartilaginous or "fibrovesicular" patelloids in some reptiles
247 such as turtles and crocodiles (Haines 1940; Haines 1942; Pearson & Davin 1921a; Pearson &
248 Davin 1921b), but these are not well-explored. Thus, although such fibrous tissues seem to be
249 excellent candidates for intermediate evolutionary character states between "absence of ossified
250 patella (normal extensor tendon)" and "presence of ossified patella", empirical grounding for this
251 transformational sequence within Sauropsida is weak.

252 No patella has been observed in early, stem-group birds throughout the Jurassic and Cretaceous
253 periods, except in the well-documented Cretaceous Hesperornithes, diving birds with vestigial
254 wings and an extremely large and unusually shaped patella, resembling that in some extant diving
255 birds (Lucas 1903; Marsh 1875; Martin 1984; Martin & Tate 1976; Shufeldt 1884; Thompson
256 1890). A patella is found in some Cenozoic fossil bird specimens, most notably archaic penguins,
257 and commonly among many crown clade birds (Dye 1987; Dye 2003; Hutchinson 2001;
258 Hutchinson 2002; Ksepka et al. 2012; Shufeldt 1884; Vickaryous & Olson 2007; Walsh & Suarez
259 2006). Our recent study (Regnault et al., 2014) inferred that a patella was probably ancestrally
260 present in the common ancestor of Hesperornithes and living birds over 70 Mya. However, the
261 bony patella was lost (and in some cases replaced by fatty cartilaginous tissue) in some large

262 flightless birds such as emus, cassowaries and the extinct moa, yet unexpectedly is present as a
263 double ossification in the knee joints of ostriches (Chadwick et al. 2014).

264 An osseous patella is generally found in two of the three crown groups of Mammalia: Eutheria
265 (Fig. 3) and Monotremata (see Fig. 4A-D), but not in most Metatheria (see Fig. 4E, F) (Dye
266 1987,2003; Vickaryous & Olson 2007). This raises the question whether this patella represents
267 independent, convergent evolutionary origins in the Eutheria and Monotremata, or an ancestral
268 origin for all three groups, with loss of the ossified patella amongst most Metatheria. To address
269 this question, we conducted phylogenetic character mapping with Mesquite software (Maddison
270 & Maddison 2017) that reconstructed patellar evolution in Mammalia. Using likelihood methods,
271 we also traced the most likely pattern of evolution over existing phylogenies, and considered
272 alternate proposed topologies to test how they affected our reconstructions. Based on the
273 predicted evolutionary patterns and individual morphologies, we propose suggestions as to the
274 lifestyle of particular taxa, and consider where general correlations between lifestyle and patellar
275 presence/absence might exist (or not).

276 Mottershead called the patella "that prince among sesamoids" but questioned whether it is "not
277 typical of its kind" (Mottershead 1988). But is there even a "typical" patella (bony or otherwise)?
278 Our synthesis of key data from morphology and function to phylogeny, development and genetics
279 allows us to evaluate just how "typical" any patella is, even for a mammalian patella.

280 MATERIALS AND METHODS

281 Our methods followed standard phylogenetic character mapping (i.e. evolutionary
282 reconstructions) methods in comparative biology (e.g. Baum & Smith 2013; Cunningham et al.
283 1998; Huelsenbeck et al. 2003); with details as follow. We surveyed the literature and additional
284 specimens (Fig. 4; Table S1 and Figs. S1-S3) and coded the patella as absent (score = 0),
285 fibrocartilaginous (i.e. "patelloid"; score = 1), or ossified (score = 2) for each taxon in our
286 analysis, with "?" denoting an ambiguous character coding. We did not code the "suprapatella"
287 here as there is substantial confusion over its homology. We used two phylogenetic optimization
288 methods in Mesquite software (Maddison & Maddison 2017) to reconstruct possible evolutionary
289 polarity of the patella in the clade Mammaliamorpha (with a focus on Mammaliaformes), as
290 follows. First, for broad reconstruction across Tetrapoda, we used a phylogeny based on Gauthier
291 et al. (1988) and Shedlock and Edwards (2009), with average branch lengths they derived from
292 several studies. Some aspects of the phylogeny remain controversial, such as the position of
293 Testudines (turtles; Hedges 2012). Reconstruction was performed using Mesquite's parsimony
294 algorithm and unordered character states and results are illustrated in Figure 3. As this analysis
295 only involved major clades and not any stem lineages, it was intended as purely illustrative of
296 general patterns and the current state of knowledge, given that patellar evolution across Tetrapoda
297 had not been analyzed phylogenetically before.

298 We adopted composite phylogenetic trees for our study taxa (Archibald 1998; Beck 2012; Bi et
299 al. 2014; Cardillo et al. 2004; Forasiepi et al. 2006; Gatesy et al. 2013; Goloboff et al. 2009;
300 Kielan-Jaworowska et al. 2004; Luo et al. 2003; Luo 2007a; Luo et al. 2002; Luo 2007b; May-
301 Collado et al. 2015; Meredith et al. 2009; Meredith et al. 2011; Mitchell et al. 2014; O'Leary et al.
302 2013; O'Leary & Gatesy 2008; dos Reis et al. 2012; Rose 2006; Sánchez-Villagra et al. 2007;
303 Song et al. 2012; Spaulding et al. 2009; Springer et al. 2003; Springer et al. 2007; Springer et al.
304 2009; Thewissen 1990; Thewissen et al. 2007; Wible et al. 2007; Zack et al. 2005). As defined by

305   several authors, the clade Mammaliaformes includes crown group Mammalia plus closely related
306   extinct stem-mammals such as the iconic *Morganucodon* and the more recently discovered
307   *Sinoconodon*, and is characterised by diagnostic features involving the teeth, jaw and inner ear
308   (Kielan-Jaworowska et al. 2004; Rose 2006). Extant mammals (crown group Mammalia) include
309   three main clades: Placentalia, Marsupialia and Monotremata. Placentalia lie within the Eutheria;
310   Marsupialia lie within the Metatheria, and Monotremata lie within the Australosphenida, all of
311   which diverged during the Mesozoic, pre-dating the K-Pg extinction event ~66 Mya.

312   The overall phylogeny used for Mesozoic mammals (Fig. 5) was based on the topology of Bi et
313   al. (2014); their main figure 4 and extended data figure 9. However, we chose to show
314   *Henkelotherium* branching prior to *Vincelestes* following (Luo 2007) because their relationship
315   with Theria was less well-resolved in Bi et al. (2014). Approximate divergence times for key
316   clades were taken from Bi et al. (2014)'s figure 4. Divergence of *Vincelestes*, *Henkelotherium* and
317   *Akidolestes* came from Luo (2007). The remaining undated divergences and branch lengths ere
318   estimated using data from the Paleobiology database (fossilworks.org), accounting for the date
319   ranges of fossil taxa.

320   The topology of the metatherian tree was based on several sources that are all fairly congruent
321   with one another. *Sinodelphys* was least nested, as in Luo et al. (2003), followed by *Asiatherium*,
322   *Pucadelphys + Mayulestes*, *Herpetotherium*, and crown Marsupalia as shown by Sánchez-
323   Villagra et al. (2007) (also by Beck 2012; Luo et al. 2003). Sparassodonta were sister to crown
324   Marsupialia (Babot et al. 2002; Forasiepi et al. 2006; Suarez et al. 2016). The topology and
325   divergence dates of crown Marsupialia were from Mitchell (2014). Divergence dates of
326   *Sinodelphys*, *Asiatherium*, and of *Pucadelphys* from *Mayulestes* were from Luo et al. (2003).
327   Dates within Sparassodonta were taken from Forasiepi (2009). The remaining undated nodes
328   were estimated, so that the interbranch lengths between dated nodes was approximately equal.

329   The topology of basal eutherians used Hu et al.'s (2010), with *Juramaia* polytomous with *Eomaia*
330   and crown Placentalia as in Luo et al. (2011), which also brought the basal eutherian node back to
331   ~160mya. Alternative placement of *Eomaia* as a stem therian (as in O'Leary et al. 2013) was also
332   explored as a supplementary analysis. The branch order of the main crown Placentalia clades
333   (Xenarthra, Afrotheria, Euarchontoglires, and Laurasiatheria), as well as the placement of many
334   of the extant and fossil groups, came from O'Leary et al. (2013). Divergence dates of extant taxa
335   were estimated from the Timetree database Timetree.org (Hedges et al. 2006). Divergence dates
336   of fossil taxa were from O'Leary et al. (2013) or estimated from fossil dates from the
337   Paleobiology database as above.

338   Exceptions and expansions to the topology of O'Leary et al. (2013) were as follows: (1) The
339   placement of Pantodonta and Taeniodonta is ambiguous, but both groups were suggested to be
340   derived from the cimolestids (McKenna & Bell 1997). Here we placed these groups as stem
341   eutherians (Rook & Hunter 2014). (2) Within primates, we placed *Omomys*, *Teilhardina*,
342   *Archicebus*, *Notharctus* and *Plesiadapis* (Ni et al. 2013). (3) Within Glires, *Nonanomalurus* was
343   classified with Anomaluroidea, diverging from the group containing Sciuridae (Marivaux et al.
344   2016), and adopting a divergence date of 60MYA. Apatemyids like *Apatemys chardini* may be
345   basal members of Euarchontoglires, with weak support for a sister-group relationship with Glires
346   (Silcox et al. 2010). (4) The topology within Carnivora was based on Flynn et al. (2005). (5) The
347   detailed topology within Cetartiodactyla followed Spaulding et al. (2009). *Maiacetus* was placed
348   alongside *Rodhocetus* and *Artiocetus* (within Protocetiidae). *Gervachoerus* was placed tentatively
349   alongside *Diacodexis* (as it is classified within Dichobunoidea); its actual placement is unclear.

350   *Paratylopus*, *Merychyus* and *Protoreodon* were placed near to *Camelus*, within Camelidamorpha,
351   but again their exact relationships are unclear. (6) The detailed topology of Perissodactyla
352   followed Holbrook & Lapergola (2011). Notoungulata and *Eoauchenia* (Litopterna) were placed
353   sister to Perissodactyla (Welker et al. 2015). Following recent analyses (e.g. Cooper et al. 2014),
354   we placed Phenacodontidae and Desmostylia as stem perissodactyls. (7) The position of
355   Dinocerata is controversial. Here we placed Dinocerata within Laurasiatheria, close to
356   Perissodactyla and Cetartiodactyla (Burger 2015), until more data on the placement of this group
357   becomes available. (8) The detailed topology within Chiroptera followed Simmons et al. (2008).

358   Our analysis involved numerous challenges and caveats. Many anatomical studies of extant or
359   extinct species omit any mention of the patella, leaving its provenance in these taxa as uncertain.
360   Interpretation of patellar status is especially challenging in fossils due to the rarity of finds with
361   extensive, articulated postcranial material, the potential occurrence of other small non-patellar
362   bones in the knee joint, and the uncertain age of the animal at time of death versus the
363   developmental timing of sesamoid ossification (usually unknown; often relatively late in
364   ontogeny). For the present analysis, statements in the primary literature regarding patellar status
365   were generally accepted at face value except when superseded by more recent observations. From
366   some publications with high quality photographs, patellar status was tentatively interpreted even
367   if not discussed in the original text. In some cases, patellar status was confirmed by direct
368   observation (e.g. Fig. 4; Figs. S1-S3; Table S1). Drawings found in secondary citations were
369   mostly not been taken as definitive evidence, as we noticed examples of discrepancies between
370   primary references and such drawings found in review articles or even textbooks, which may
371   simply assume patellar status in mammals. Also, many mammalian groups are found over long
372   temporal and geological spans, thus we were cautious about using the presence of a patella in one
373   or a few individual extant or fossil specimens to infer presence throughout the group, although in
374   some cases there was clearly enough conservatism within a clade to score it for all members.

375   An important knee structure related to the patella is the femoral patellar or intercondylar sulcus
376   (groove) (Norell & Clarke 2001; Polly 2007). This sulcus is anatomically associated with a true
377   patella (Figs. 1,4) in terms of its direct role in guiding the patellar sesamoid and tendon's path of
378   movement during leg flexion/extension, and in mediolaterally confining the patellar tendon,
379   which may enhance osteogenic stresses favouring the formation of a patella (Sarin & Carter
380   2000b; Wren et al. 2000). In the absence of an observed patella in fossil specimens, this sulcus at
381   the distal end of the femur is sometimes treated as evidence of a patella even in the absence of the
382   observed bone itself. We deemed this conclusion to be unwarranted. For example, the evolution
383   of a patellar sulcus in early pygostylian birds substantially predated the evolution of an ossified
384   patella in later ornithurine birds; moreover the sulcus was retained in some avian taxa that lost the
385   patella (Clarke & Norell 2002; Hutchinson 2002; Livezey & Zusi 2006; Regnault et al. 2014). In
386   contrast, a prominent sulcus is absent in many Squamata despite the presence of a patella (S.R.
387   and J.R.H., pers. obs.). Together these observations indicate that these two anatomical features
388   are not obligatorily coupled, so reliance on the observed presence of an ossified patella in fossil
389   specimens was warranted. Nonetheless, at least among mammals the complete absence of a
390   femoral patellar sulcus might be indicative of the absence of an ossified patella (Chester et al.
391   2012).

392   RESULTS AND DISCUSSION

393 Our overall evolutionary reconstruction of the patella for Mesozoic mammals is shown in Fig. 5,
394 for Metatheria/Marsupialia in Fig. 6, and for Cenozoic Eutheria/Placentalia in Fig. 7, with details
395 for specific taxa in Table S1 and alternative phylogenetic analyses in Figs. S4 and S5. Here we
396 sequentially summarize and discuss our findings for five subgroups of Mammaliamorpha
397 (especially Mammaliaformes): (1) Mesozoic pre-therians and stem-therians; (2) Mesozoic
398 Metatheria and Eutheria; (3) Cenozoic Monotremata; (4) Cenozoic Metatheria, and (5) Cenozoic
399 Eutheria. We then conclude with a general synthesis of our study's insights (as well as
400 uncertainties) and a consideration of how available and emerging data on developmental genetics
401 of the patella might help shed light on the "evo-devo" of the patella, augmenting the phylogenetic
402 and anatomical insights that this study focuses on.

403 *1. Mesozoic pre-therian and stem-therian mammals*
404 The earliest mammals as widely construed include *Sinoconodon*, the Morganucodonta and
405 Docodonta. These were mostly small, probably insectivorous animals, that appear to have lacked
406 a patella, although it is unclear whether the known specimens contain sufficient postcranial
407 material or are from verified adults, to allow for definitive conclusions. The absence of a clear
408 patella in two stunningly preserved docodonts (the scansorial [climbing-adapted] *Agilodocodon*
409 and fossorial [digging-adapted] *Docofossor*) lends credence to the conclusion that it was
410 generally absent in early mammaliaforms (Luo et al. 2015b; Meng et al. 2015). There is
411 convincingly strong evidence of absence of a bony patella in earlier pre-mammals in lineages
412 dating from the divergence of Synapsida and Sauropsida/Reptilia (~320 Mya), including the early
413 "pelycosaurs", therapsids and cynodonts (Kemp 2005).

414 Australosphenida, the clade containing and thus ancestral to extant Monotremata, diverged from
415 other mammals extremely early, possibly in the mid-Jurassic (Kielan-Jaworowska et al. 2004).
416 There is little postcranial material for any extinct members of this lineage however, and no
417 hindlimbs (Kemp 2005). The patella in crown clade monotremes is discussed below.

418 *Fruitafossor,* from the late Jurassic (150 Mya), diverged after the Australosphenida (Luo & Wible
419 2005). Its relationship to other early mammals is complicated by its mixture of characters in the
420 molar teeth, middle ear and elsewhere. *Fruitafossor* is described as lacking a patella, and it is
421 proposed to have had a fossorial lifestyle.

422 The Eutriconodonta were found abundantly across the world from the middle Jurassic to early
423 Cretaceous periods (Kielan-Jaworowska et al. 2004). Among eutriconodonts, a poorly developed
424 patellar groove on the distal femur is found but an ossified patella is absent.

425 The Allotheria were an extremely successful and widely dispersed group of mammals, among
426 which the best understood are the multituberculates (Kielan-Jaworowska et al. 2004; Wilson et al.
427 2012). Generally Allotheria are found from the late Triassic to the Eocene; thus this group
428 spanned the heyday of the non-avian dinosaurs and survived the K-Pg extinction (Kielan-
429 Jaworowska et al. 2004). Multituberculates were predominantly small animals, either herbivorous
430 or omnivorous (Kielan-Jaworowska et al. 2004). A patella is noted for the nearly complete
431 multituberculate *Ptilodus*, a proposed scansorial animal from the early Cenozoic. A patella is also
432 present in the Cretaceous multituberculate *Chulsanbaatar*. It is unclear whether a patella is
433 typical of all members of the multituberculate group and is under-reported due to lack of
434 hindlimb material for most group members, or whether it occurs only among selected species,
435 although the former seems more plausible. A patella is not reported, however, for the early
436 Jurassic basal *Rugosodon*, a proposed multituberculate specimen with one relatively intact knee

437   joint (Yuan et al. 2013), so it is conceivable that an ossified patella evolved later within the
438   Allotheria (Fig. 5).

439   Specimens of the diverse group "Haramiyida" are mostly restricted to cranial material, and the
440   relationship of this ancient group to other Allotheria and Mammaliaformes has been controversial
441   (Butler 2000; Kielan-Jaworowska et al. 2004; Rose 2006). However, several recently described
442   more complete haramiyid specimens from the Jurassic with at least one preserved knee joint lack
443   a patella (Bi et al. 2014; Zheng et al. 2013; Zhou et al. 2013). These new specimens have been
444   interpreted to support an Allotheria clade including a paraphyletic "Haramiyida" (but a valid
445   clade Euharamiyida including many "haramiyid" taxa) and Multituberculata (Fig. 5), although
446   new analyses of a key specimen of *Haramiyavia* concluded that the haramiyids and
447   multituberculates were not closely related (Luo et al. 2015a). The inclusion of the
448   "Euharamiyida" in Allotheria pushes the divergence date of the group significantly earlier into
449   the late Triassic, whereas multituberculates themselves appear only in the middle to late Jurassic.
450   Final resolution of this controversy will undoubtedly require additional fossil material.

451   Symmetrodonta were a group of diverse, small mammals widely distributed in time from the late
452   Triassic to the late Cretaceous (Kielan-Jaworowska et al. 2004). In the subgroup of
453   spalacotheroids, a patella is reported for one fairly complete specimen (*Zhangheotherium*) but not
454   for another (*Akidolestes*) (Chen & Luo 2012; Luo & Ji 2005) (these two specimens are coded
455   oppositely in character matrices in some subsequent publications (Bi et al. 2014; Zhou et al.
456   2013), probably in error); a patella seems absent in *Maotherium*.

457   Eupantotheria was a diverse group found commonly from the mid-Jurassic to the early
458   Cretaceous (Kielan-Jaworowska et al. 2004). The patella is reported as absent in both an early
459   European specimen (*Henkelotherium*, late Jurassic) and a later South American specimen
460   (*Vincelestes*, early Cretaceous) (Fig. 5). The large group of dryolestid Eupantotheria possibly
461   survived past the K-Pg boundary, have an unknown patellar status.

462   The tribotherians were the earliest-diverging group to share key molar features with the therians.
463   However, no postcranial specimens have been reported; thus nothing is known of their patellar
464   morphology (Kielan-Jaworowska et al. 2004).

465   The single specimen of *Juramaia* from the Jurassic (~160 Mya) unfortunately lacks hindlimb
466   material; therefore its patellar status is unknown. Based on its forelimb, *Juramaia* is proposed to
467   have been scansorial or possibly arboreal (Luo et al. 2011). The later specimen of *Eomaia* from
468   the early Cretaceous includes all limb elements, and is described with a patella (Ji et al. 2002).
469   Based on limb and foot features, *Eomaia* was probably scansorial or arboreal. In the original
470   publication, *Eomaia* was described as the earliest eutherian mammal (Fig. 5), however a more
471   recent and much more extensive analysis confidently placed *Eomaia* prior to the
472   eutherian/metatherian divergence (O'Leary et al. 2013) and thus at least as a stem member of the
473   clade Theria (see Fig. S4). *Eomaia* (and presumably *Juramaia*) postdate the divergence of the
474   Symmetrodonta, but their positions relative to the Eupantotheria remain to be determined, as does
475   any close relationship between these two key taxa. Lacking a better alternative, here we refer to
476   these taxa as "Theria", and in Fig. 5 vs. Fig. S4, consider the consequences of *Eomaia*'s
477   phylogenetic position on our conclusions.

478   In surveying the available data mapped onto our composite phylogeny (Figs. 5, S4), it becomes
479   evident that an ossified patella evolved multiple times (at least four) along the mammalian stem

480   lineages during the Mesozoic era, whether using parsimony or maximum likelihood optimisation
481   methods: at some highly uncertain time in the long mammalian lineage that led to Monotremata,
482   in multituberculates/Allotheria, in *Zhangheotherium* or a direct ancestor, and likely twice (or
483   between one to three times, depending on the placement of *Eomaia*; see Figs. 5 and S4) in the
484   clade containing *Eomaia* and Theria (Metatheria and Eutheria). This result remained the same if
485   the Euharamiyida were not included with multituberculates but pre-dated crown Mammalia, as
486   suggested by some recent studies (e.g. Luo et al. 2015a).

487   *2. Mesozoic Metatheria and Eutheria*
488   The two major extant mammalian groups, the Metatheria and Eutheria (together forming the
489   clade Theria), diverged as early as the Jurassic (Fig. 5). The earliest fossil identified as stem
490   metatherian, *Sinodelphys*, dates from the early Cretaceous of China (125 Mya, approximately
491   contemporary to *Eomaia*), and lacks a patella (Luo et al. 2003). A patella also seems absent in the
492   less complete Cretaceous stem metatherian *Asiatherium* (Szalay & Trofimov 1996).

493   The earliest known occurrences of the patella in definitive stem eutherians (Figs. 5,7) were in the
494   late Cretaceous *Ukhaatherium* (Horovitz 2003), a relatively unspecialized form, and in
495   *Zalambdalestes* (Wible et al. 2005), a more specialized taxon sometimes described as resembling
496   later lagomorphs (Rose 2006). Patellar status at the crown group node for Theria (plus *Eomaia*)
497   remains ambiguous (Figs. 5,6,S4), as we consider below.

498   *3. Cenozoic Monotremata*
499   The origins of the Monotremata (egg-laying mammals) are poorly understood. They are
500   considered extant members of the clade Australosphenida (the alternative term Prototheria has
501   been superseded), and hence with early roots in the Mesozoic. Molecular studies based on the
502   sequenced genome of the platypus corroborate the long held interpretation that the monotremes
503   diverged prior to the metatherian/eutherian split, consistent with proposed fossil-based
504   phylogenies (Warren et al. 2008). Unfortunately, there are almost no reported hindlimb specimens
505   of any extinct monotreme (including probable early monotreme fossils found in South America;
506   (Musser 2003)), with the exception of the Pleistocene *Zaglossus* (echidna) from Australia and
507   New Guinea (which may be the same as the extant species of that name). Unfortunately, although
508   fossil *Zaglossus* hindlimb elements exist, including an articulated knee, neither presence nor
509   absence of the patella has been reported (Murray 1984). The extant monotremes, the platypus
510   (*Ornithorhynchus anatinus*) and the echidnas (Tachyglossidae, two genera *Zaglossus* and
511   *Tachyglossus*; four known species) all have substantial patellae (see Fig. 4A, B, C, D) (Herzmark
512   1938; Rowe 1988). It is unclear when the two extant monotreme genera diverged, although a date
513   early in the Cretaceous has been proposed (Rowe et al. 2008), and it is impossible for now to date
514   the appearance of the patella in the monotreme lineage. Regardless, an ossified patella is
515   homologous for this crown clade (Fig. 5), and alternative phylogenetic topologies did not change
516   the general pattern of patellar evolution (Fig. S4).

517   *4. Cenozoic Metatheria*
518   All extant Metatheria are within the subgroup of Marsupialia, however non-marsupials did exist
519   earlier during the Cenozoic. As documented in the pioneering study of sesamoids in Marsupialia
520   by Reese et al. (2001), an ossified patella seems to be absent in the great majority of extant
521   marsupial species, both from Australia and the Americas (Flores 2009; Herzmark 1938; Holladay
522   et al. 1990; Reese et al. 2001; Rose 2006; Rowe 1988), including the sole surviving North
523   American marsupial, the opossum *Didelphis virginiana* (Fig. 4E, F). Many marsupials have other
524   sesamoid bones in the knee region (e.g. the parafibula, lateral sesamoid, or "sesamoid bone of

525   Vesalli"; Fig. 1), as well as a fibrocartilaginous "patelloid", which may to some degree serve the
526   mechanical function of a bony patella (Reese et al. 2001). However, the mechanics of a fibrous or
527   bony patella remain essentially unstudied (to our knowledge) in non-placental mammals, so this
528   is simply speculation. Studies have claimed some association between reduction of the patella in
529   many marsupials and locomotor style or ecology (Holladay et al. 1990; Reese et al. 2001), but
530   these deserve testing with more detailed sampling across phylogeny and ontogeny.

531   Nonetheless, an ossified patella is found in a small number of extant marsupial species among
532   otherwise divergent clades, both from Australia: at least several Peramelidae or bandicoots, and
533   the two marsupial mole species of *Notoryctes*); and from South America: *Tarsipes*, a honey
534   possum; and several, and possibly all, Caenolestidae or shrew opossums (see Fig. 6: note collapse
535   of several large clades in terms of total number of species, in which no species have been shown
536   to possess a bony patella; Table S1).

537   Possibly uniquely among crown clade marsupials, bandicoots also possess a chorioallantois fused
538   to the uterine epithelium (i.e. a true placenta) (Freyer et al. 2003; Padykula & Taylor 1976),
539   which combined with an osseous patella led to the initial suggestion that they might actually be
540   eutherians (Reese et al. 2001). However, more recent molecular and fossil-based phylogenetic
541   studies provide no support for that hypothesis of eutherian bandicoots (Asher et al. 2004;
542   Meredith et al. 2008b; Sanchez-Villagra et al. 2007; Westerman et al. 2012). Bandicoots clearly
543   are metatherians, and their chorioallantois is thus a convergently evolved trait rather than
544   plesiomorphic. It remains to be determined whether an ossified patella is present in all or only
545   some bandicoots, as so far it is only reported in the Peramelinae of dry or temperature forests of
546   Australia, not yet in the Peroryctinae of tropical rainforests of New Guinea, or the more distantly
547   related bilbies (Groves & Flannery 1990; Meredith et al. 2008a; Westerman et al. 2012).
548   Similarly, a comprehensive study of the Caenolestidae remains to be performed, much as a more
549   thorough study of the major marsupial clade Diprotodontia (wombats, kangaroos and kin) is
550   needed.

551   Not surprisingly given the absence of a bony patella in most extant marsupials, any evidence of a
552   patella is absent in the early Cenozoic Metatheria *Pucadelphys, Mayulestes,* and the later
553   *Herpetotherium*. Unexpectedly, a bony patella is reliably reported in the Borhyaenoidea, an
554   unusual group of dog-like carnivorous South American marsupials found from the Palaeocene
555   through the Miocene (Argot 2002; Argot 2003a; Argot 2003b; Argot 2003c; Argot 2004; Argot &
556   Babot 2011; de Muizon et al. 1997). Patellar status in some members of Borhyaenoidea (e.g.
557   *Borhyaena* itself and *Lycopsis* (Argot 2004)), and in the more inclusive group Sparassodonta, is
558   uncertain due to the incomplete state of specimens. Szalay and Sargis (2001) noted other
559   enigmatic fossil patellae from the Palaeocene of Brazil that they assigned to Metatheria, but the
560   phylogenetic relationships of those fragmentary remains are unclear and no patellae were shown.
561   However, no ossified patella is reported in extant or recent carnivorous marsupials such as
562   *Thylacinus*.

563   Two related, pernicious problems remain for interpreting the evolution of the patella in
564   Metatheria that may have ramifications for all of Mammalia/Mammaliaformes. First, Szalay and
565   Sargis (2001:pp.164-5) reported the presence of an ossified patella in older individuals of
566   *Didelphis virginiana* in their study of an ontogenetic series from this species. They stated (p.165)
567   "In older individuals there is occasionally an elongated and small sesamoid ossification within
568   the tendon of the quadriceps femoris where it crosses the knee joint when the knee is flexed."
569   However, this observation was not documented with illustrations or photographs (especially

570   tissue histology or x-rays) and hence remains a tantalizing anecdote. Similarly, Owen (1866)
571   commented that some marsupials had no ossifications in their patellar tendon but others had
572   "only a few irregular specks of ossification" and a "distinct but small bony patella in the
573   *Macropus Bennettii*." In contrast, Reese et al. (2001) and Holladay et al. (1990) respectively
574   sampled 61 specimens (~39 adults) from 30 species of marsupials and 3 macropodid specimens
575   (of unknown maturity), documenting no ossified patellae except as noted in bandicoots, and their
576   studies used clear methods for identifying ossified tissues. It remains possible that patellar
577   ossification occurs variably in older individuals among Metatheria, which would help explain its
578   patchy description in known taxa.

579   If the latter situation is the case (i.e. the literature is unclear about patellar ossification in
580   marsupials because they have more inherent variability), then it relates to a second problem, a
581   cladistic one of character coding and transformational homology (*sensu* Brower & Schawaroch
582   (1996); Pinna (1991)). Should character states of the patella in metatherians, or even all mammals
583   and their kin, be coded as an ordered transformational series such as absent (0), fibrocartilaginous
584   (1) or ossified (2), or as an unordered series (i.e. should evolutionary steps be required to go from
585   0-1-2 as 2 steps, or unordered allowing 0-2 transformations as 1 step)? We chose the unordered
586   character option by default for all crown group mammals, but where relevant explain how an
587   ordered option changed (or did not change) our results. An endochondral ossification of the bony
588   patella is certain, but a fibrocartilaginous or otherwise soft tissue composition of the patella
589   (coded as state 1) in adults is not unambiguously the necessary (i.e. ordered) evolutionary
590   precursor character state to state 2 (ossified patella in adults). The solution to both of these
591   problems lies in more developmental data for the patella (bony and otherwise) in diverse
592   mammalian species, in addition to more scrutiny of the adult morphology in extant and fossil
593   Mammalia (especially Metatheria).

594   As noted briefly in the Introduction, many marsupials have a primarily fibrocartilaginous
595   patelloid in place of an ossified patella and some other mammals may have a "suprapatella". The
596   developmental and evolutionary relationships of these structures remain somewhat unclear,
597   particularly as some marsupials with an ossified patella (e.g. bandicoots) also possess a patelloid
598   (Reese et al., 2001), suggesting that the patelloid is not developmentally equivalent to the patella
599   in marsupials (Vickaryous & Olson 2007). If so, this would indicate independent evolutionary
600   histories of these two structures. Further work is required to clarify the relationships of the
601   patelloid and suprapatella at least in extant taxa, before definitive evolutionary trajectories can be
602   inferred. We reiterate that, just because a patella-like structure is not ossified, that does not mean
603   it is a distinct organ deserving a new name and different homology as a phylogenetic character—
604   although it may be a distinct state of the character "patella". However, either of these two
605   possibilities needs careful testing particularly for Metatheria.

606   A non-osseous patelloid/suprapatella is also found in several closely related modern placental
607   clades that lie far from the base of Eutheria (Fig. 7), suggesting that these represent independent
608   acquisitions. We have not attempted to explicitly reconstruct the evolution of the patelloid in
609   Eutheria. Lewis (1958) and Broome and Houghton (1989) speculated that the mammalian
610   patelloid might be a precursor to the tibial epiphysis (Broome & Houghton 1989; Lewis 1958) --
611   a so-called "traction epiphysis" (Vickaryous & Olson 2007). Yet considering that the patelloid
612   evolved after the tibial tuberosity (and proximal tibial epiphysis as well as distal femoral
613   epiphysis; Carter et al. 1998) of mammals, not before it, and lies proximal rather than distal to the
614   patella, we reject this hypothesis. More study of the evolution of mammaliaform long bone
615   epiphyses, however, is warranted to strongly and more generally test for associations between

616 any epiphyses and sesamoids. Furthermore, this same phylogenetic evidence indicates that the
617 patelloid in Euarchontoglires, some Carnivora and bandicoots is not ancestrally associated with
618 leaping or other behaviours (e.g. Jungers et al., 1980). As Walji & Fasana (1983) caution, the
619 ancestral mechanical environment of the patelloid/suprapatella and its roles in different
620 behaviours remain unclear, although it does seem to be associated with knee hyperflexion like a
621 typical fibrocartilaginous "wrap-around" tendon (e.g. Ralphs et al. 1991; Alexander & Dimery,
622 1985).

623 Our unordered parsimony reconstruction (Fig. 6) indicated that an ossified patella was absent in
624 the ancestor of Metatheria, then evolved in the ancestor of Sparassodonta and Marsupialia. The
625 bony patella may have been lost in the basal lineages of Marsupialia (reconstructed state here was
626 equally parsimonious between an ossified and fibrocartilaginous patella), with subsequent re-
627 acquisition in certain groups (Tarsipedidae, and possibly Notoryctidae and Thylacomyidae +
628 Peramelidae, and Tarsipedidae) (Fig. 6). Ordered parsimony reconstruction resulted in subtle
629 differences; making some nodes less ambiguous (i.e. state 1 [patelloid present] within basal
630 Marsupialia) and others more ambiguous (such as the ancestor of Sparassodonta and Marsupialia,
631 which became equally parsimonious between states 1 and 2). In contrast, maximum likelihood
632 reconstruction indicated a single origin of the osseous patella in Metatheria (Fig. 6), with
633 reduction to a fibrocartilage patelloid (in Didelphidae and the clade containing
634 Pseudocheiridae+Vombatidae) and re-acquisition of a bony patella (in Tarsipedidae) marginally
635 more likely than multiple instances of ossified patella evolution. Because presence of a patelloid
636 has not been clearly excluded in some extant marsupials (e.g. Petauridae, Acrobatidae) and is
637 unlikely to be fossilised, its reconstruction must be treated carefully. Finally, alternative
638 placement of Microbiotheriidae did not drastically alter our evolutionary reconstructions (Fig.
639 S5), aside from making a single origin of the ossified patella slightly more likely. Overall, we
640 caution that inferences about the evolutionary history of the patella in Metatheria must remain
641 tentative until further data become available.

642 *5. Cenozoic Eutheria*
643 The Placentalia include all extant Eutheria as well as some fossil stem taxa (Fig. 7). Although
644 there is some fossil evidence for placentals pre-dating the K-Pg event (Archibald et al. 2011), as
645 well as substantial molecular dating consistent with an older placental radiation, the timing of the
646 placental radiation remains highly controversial. However, our major conclusions about patellar
647 evolution in placentals are not dependent on how this controversy is ultimately resolved, as a
648 recent large-scale phylogenetic analysis convincingly established the presence of an osseous
649 patella as a derived character state in the ancestral placental irrespective of its true date of
650 divergence (O'Leary et al. 2013).

651 Fossil evidence supports the presence of the bony patella in essentially all Cenozoic placental
652 groups (Fig. 7; also see Table S1 and Figs. S1-S4, with citations therein). Specimens with
653 sufficient hindlimb material to make a determination of patellar status are rare in the early
654 Cenozoic Palaeogene period (~66-23 Mya), but Palaeocene groups in which an ossified patella
655 has been reported include the Taeniodonta (small to medium sized fossorial animals), Pantodonta
656 (early herbivores), Palaeanodonta (small, possible insectivores; perhaps related to pangolins),
657 "Condylarthra" (a diverse assemblage of putatively related taxa, probably polyphyletic, including
658 both herbivores and carnivores, many of which may be stem members of subclades within the
659 placental crown group), and the Plesiadapiformes, a sister group to crown clade primates (and
660 possibly members of the clade Primates as well) (Bloch & Boyer 2007; Silcox 2007). In general,

661 the evolutionary relationships between Palaeocene taxa and more recent placentals remain
662 enigmatic.

663 Eocene placentals include examples whose close relationships to modern groups are well
664 accepted. Among Eocene groups (Fig. 7, Table S1), an osseous patella has been reported in older,
665 extinct groups such as "Condylarthra", Creodonta (carnivores), Mesonychia
666 (carnivorous/omnivorous artiodactyls or cetartiodactyls), Dinocerata (large hippo/equid-like
667 herbivores), Brontotheriidae (large rhino-like herbivores), and Notoungulata (diverse South
668 American hoofed herbivores; probably related to Afrotheria) (O'Leary et al. 2013), as well as in
669 extinct species (in parentheses, see Table S1 for citations) recognized as stem members of several
670 extant groups: Glires (*Rhombomylus*), Perissodactyla (*Propalaotherium*), early Sirenia retaining
671 hindlimbs (*Pesoziren, Protosiren*), Proboscidea (*Numidotherium, Moeritherium, Barytherium*),
672 Rodentia (the horse-sized *Pseudotomus, Paramys*), Pholidota (*Eomanis*), Artiodactyla
673 (*Gervachoerus*), early Cetacea retaining hindlimbs (*Maiacetus*) and Chiroptera (*Icaronycteris,
674 Tachypteron*). A bony patella is also reported for several Eocene primates, including the lemur-
675 like Notharctidae (*Northarctus*) and the tarsier-like *Omomys* and *Archicebus*, in addition to the
676 enigmatic primate *Darwinius*.

677 Despite an extensive literature search, we found no reports attesting to the presence of an osseous
678 patella in certain widely cited Paleocene and Eocene species, including: *Protungulatum*,
679 frequently cited as the earliest true placental; *Miacis, Vulpavus, Viverravus* and *Didymictis*, which
680 were stem Carnivora (Gregory 1920; Heinrich & Houde 2006; Heinrich & Rose 1995; Heinrich
681 & Rose 1997; Samuels et al. 2013); *Pakicetus*, a fully quadrupedal early cetacean (though
682 sometimes reconstructed with a bony patella as in Fig. 7 and Fig. S1 M, N) (Thewissen et al.
683 2001); *Leptictis*, possibly related to crown clade lagomorphs (Rose 1999); *Sinopa*, a creodont
684 (Matthew 1906); and the early primates *Adapis, Leptadapis, Teilhardina*, and *Cantius* (Dagosto
685 1983; Gebo et al. 2012a; Gebo et al. 2012b; Rose & Walker 1985; Schlosser 1887; Szalay et al.
686 1975). There is no reason to expect that a bony patella is missing in these species. These absences
687 are more likely due to incompleteness of the fossil record and/or literature descriptions and
688 images. Moreover, the massive collections of Eocene specimens from the Messel and Green
689 River lagerstätten in Germany and Wyoming have not yet been fully described (Grande 1984;
690 Schaal & Ziegler 1992). There are many examples of an ossified patella in specimens from extant
691 placental groups across the more recent Miocene, Oligocene, Pliocene and Pleistocene, but a
692 comprehensive search of the literature for those geologic epochs was deemed redundant for our
693 major conclusions.

694 Based on fossil/morphological evidence plus extensive genomic DNA sequencing, there is a
695 consensus that crown clade placentals can be historically and geographically defined by four
696 major groups: Xenarthra, Afrotheria, Euarchontoglires (further divided into Euarchonta; featuring
697 Primates; and Glires) and Laurasiatheria (Rose 2006). These in turn may be resolved, with
698 somewhat less consensus, into 19 crown clade "orders" (Fig. 7) (O'Leary et al. 2013). In two of
699 these orders, the afrotherian clade Sirenia and the cetacean branch of (Cet)artiodactyla
700 (laurasiatherian clade), extant members have extensively reduced or absent hindlimbs and thus
701 lack skeletal knee structures, including an osseous patella. In contrast, the bony patella is retained
702 among the aquatic seals and sea lions in Carnivora, although unlike Sirenia and Cetacea these
703 animals still display some terrestrial habits and thus presumably still employ the gearing
704 mechanism that the patella is involved in at the knee. An ossified patella is documented as present
705 in at least some members of all other 17 placental "orders" (e.g. Figs. 4G,H,7,S1-S3; Table S1)

706   (de Panafieu & Gries 2007; De Vriese 1909; Dye 1987; Herzmark 1938; Lessertisseur & Saban
707   1867; Rose 2006).

708   The evolution of the Cetacea presents an interesting scenario regarding patellar evolution (Fig. 7).
709   Cetaceans evolved from a common ancestor with other (cet)artiodactyls (Spaulding et al. 2009;
710   Thewissen et al. 2007). Early artiodactyls (including cetaceans), such as *Diacodexis* and
711   *Indohyus*, shared morphological similarities with both extant groups of Cetacea (toothed and
712   baleen whales) and yet retained an osseous patella (Rose 1982; Thewissen et al. 2007), much as
713   stem Sirenia did (Domning 2001; Zalmout 2008). Patellar status in *Pakicetus*, a presumptive
714   early cetacean with full hindlimbs, remains uncertain based on the primary literature, but
715   presence is likely considering the presence of a bony patella in its closest relatives. *Rodhocetus*
716   and *Ambulocetus*, probably semi-aquatic early cetaceans, still had large hindlimbs and ossified
717   patellae (Madar et al. 2002). The pelvis and hindlimbs are greatly reduced in the later cetaceans
718   *Dorudon* and *Basilosaurus*, but a bony patella is still present in these animals (Gingerich et al.
719   1990; Uhen 2004). It is not clear exactly when the patella was lost altogether in later cetaceans
720   with increasingly reduced hindlimbs.

721   Bats present another interesting case of patellar evolution (Fig. 7; Table S1). An osseous patella is
722   generally present in bats (Pearson & Davin 1921b). A bony patella is also reported in a well-
723   preserved hindlimb of an early Eocene bat, *Icaronycteris*, of intermediate form but proposed to be
724   a microchiropteran (Jepsen 1966). However, in studies of multiple genera of modern bats
725   including members from both of the major subgroups Megachiroptera and Microchiroptera
726   (which is possibly paraphyletic), a bony patella was noted as absent in four species of the
727   megachiropteran *Pteropus* (flying foxes of various sizes), and a few individual species of
728   *Cephalotes, Epomophorus and Vespertilio* (De Vriese 1909; Lessertisseur & Saban 1867; Smith
729   et al. 1995). No obvious lifestyle distinction was noted for the *Pteropus* genus as compared to
730   many other bats, hence the loss of the ossified patella in members of this particular subgroup (and
731   others) remains mysterious. In general, bat hindlimbs are highly derived, adapted to hanging and
732   pulling rather than pushing. A few bats such as the vampire bats are actively quadrupedal (Adams
733   & Thibault 2000; Riskin & Hermanson 2005). Bat hindlimbs are articulated in abduction, so that
734   the knee faces dorsally; as in the original ancestral orientation for Tetrapoda (Fig. 2) (Neuweiler
735   2000; Schutt & Simmons 2006). There remains a need for a comprehensive study of the patella in
736   bats (Smith et al. (1995) only studied 31 specimens of 13 species), but this is challenging due to
737   the existence of >900 extant bat species (Jones et al. 2002). The microstructure of the "patelloid"
738   in *Pteropus* is generally similar to that in many marsupials (e.g. deep layer of fibrocartilage;
739   superficial layer of dense connective tissue contiguous with the quadriceps/patellar tendon)
740   (Smith et al. 1995). This also raises the question of whether the patella only ossifies later in
741   adulthood in *Pteropus*, rather than not ossifying at all.

742   *General evolutionary patterns and ambiguities*
743   Considering the above distributions of patellar presence/absence in Mammalia (Figs. 5-7; Figs.
744   S4,S5) and our data matrix (Table S1), the simplest interpretation of the evolutionary record of
745   the patella in mammals (by parsimony and maximum likelihood mapping of presence/absence) is
746   that this structure arose (i.e. ossified) independently at least four times (but possibly up to six),
747   mostly during the Mesozoic era: 1, in Australosphenida ancestral to modern monotremes; 2, in
748   Multituberculata (later than *Rugosodon*); 3, in Symmetrodonta (specifically in Spalacotheroidea
749   that were ancestral to *Zhangheotherium* but not *Akidolestes*); 4-6, in early Theria (including
750   Eutheria, Metatheria, *Eomaia* and related stem groups; depending on topology between one and
751   three times in this clade). Conceivably, a single common patelloid precursor may pre-date the

752   origins of the bony patellae, or the bony patella may have arisen fewer times and undergone loss
753   (and re-gain) in some lineages, similarly to the pattern in Metatheria. Each of these scenarios
754   remain difficult to test purely with fossil evidence, however, due to the typical lack of
755   preservation of cartilaginous or fibrous structures.

756   Once the bony patella evolved in Eutheria, it was highly conservative in its presence (Fig. 7).
757   There are very few examples of fossil or extant Eutheria in which the hindlimb remains intact but
758   the patella is unossified in adults (e.g. *Pteropus*). A caveat is that many fossil specimens are not
759   sufficiently complete for a definitive rejection of patellar ossification in those taxa. Still, the
760   evolutionary stability of the osseous patella in Eutheria stands in contrast to its general variability
761   across mammals, and suggests some conserved functional requirement and/or ontogenetic
762   mechanism that remains to be determined.

763   Although an ossified patella is absent in the majority of Metatheria, it is reported in several
764   groups (Figs. 6, S5). This likely represents some loss and regain(s) of the early metatherian bony
765   patella. Importantly, in this case the presence of a fibrocartilaginous "patelloid" in most
766   marsupials shows a clear evolutionary polarity from an ossified patella to a non-ossified
767   patelloid, and back again in the case of the secondary gain of ossification, in each case within
768   Metatheria (Reese et al. 2001). This "patella to patelloid" transition suggests the reverse may also
769   be possible – that a soft tissue patelloid may represent the evolutionary precursor to an ossified
770   patella – but it has yet to be clearly documented. There is no obvious lifestyle or biomechanical
771   correlate among all four groups of osseous patella-bearing Metatheria: the notoryctid moles are
772   underground burrowers, and bandicoots may dig for insects, but *Tarsipes* is a nectar feeder and
773   the borhyaenoids/sparassodonts were largely terrestrial carnivores. In contrast, other Australasian
774   carnivorous marsupials including the recently extinct thylacine, and the extant quoll, numbat and
775   Tasmanian devil are not reported to have a bony patella.

776   The large size of the patella in the monotreme platypus might be related to its aquatic (and partly
777   fossorial) lifestyle. The other monotremes, the echidnas, also burrow and the long-beaked species
778   (*Zaglossus*) lives in underground dens-- further suggesting an association between fossorial
779   habits and the presence or enlargement of a bony patella in Monotremata, as well as in some
780   fossil Mammaliaformes (multituberculates?) but curiously not in other fossorial stem taxa (e.g.
781   the docodont *Docofossor*). Reduction of the patella in the Cetacea and Sirenia is not intrinsically
782   correlated with their aquatic lifestyle, but with the reduction of the hindlimbs as part of their
783   particular adaptations. Elsewhere in groups with aquatic adaptations, for example in various
784   diving birds, an unusually large patella is found. It seems premature to weave detailed scenarios
785   around the high degree of convergent evolution of the osseous patella in mammals until the
786   biomechanical function and genomic control of the patella are better understood, and improved
787   phylogenetic sampling improves resolution of when it evolved in particular lineages.

788   *Patellar developmental genetics*
789   Molecular phylogenomics provides a potential independent or synergistic approach to resolving
790   issues of patellar evolution. If specific genomic sequence signatures could be associated with
791   patellar status, then comparison of the genomes of the various extant but widely separated groups
792   with a bony patella might indicate whether these represent convergence events or a common
793   ancestral event (i.e. identified via shared evolutionarily transmitted genetic markers required for
794   patellar development). For example, it has recently been shown that the ability to taste sweet
795   carbohydrates in hummingbirds represents a trait convergence. Hummingbirds diverged from the
796   insectivorous swifts, in which the sweet taste receptor is inactivated by mutations in the receptor

797   coding gene. In hummingbirds, the ability to taste sweet has been re-acquired, apparently through
798   molecular adaptation of the umami receptor to detect sweet molecules (Baldwin et al. 2014). It
799   would be helpful to understand the (developmental) genetics of the patella as a step toward the
800   identification of such sequence signatures. Developmental genetic studies in two mammals,
801   humans and mice, have identified genes required for correct patellar specification. The known
802   functions of some of these genes are informative regarding their requirements.

803   There are currently approximately 12 human genetic disorders with identified molecular bases
804   that regularly include abnormal, reduced or absent patellae (hypoplasia or aplasia) as an
805   important aspect of the phenotype (reviewed by Bongers et al. (2005), see also Warman et al.
806   (2011) and Table S2 for details). There are also several genes whose genetics in mice indicates
807   relevance to patellar development at least in rodents. A detailed discussion of all these syndromes
808   and genes is beyond the scope of this study. However, the known patella-related genes can be
809   broadly organized according to three major developmental processes: limb specification and
810   pattern formation (transcription factors such as *LMX1B, TBX4*, *PITX1* and mouse *Hoxaaccdd-11,*
811   *SOX11,* and signalling factor *WNT7A*); bone development, biochemistry and regulation (*GDF5,*
812   *CHRNG, SLC26A2, COL9A2, AKT1*); and genes involved in DNA replication and chromatin
813   (*ORC1, ORC4, ORC6, CDT1, CDC6, GMNN, CDC45, RECQL4, KAT6B, ESCO2*). Of these, the
814   genes of replication and chromatin are the most unexpected, and potentially of the most interest
815   for evolutionary studies. Patellar ossification may be dependent on the timing of DNA replication
816   in particular cells, or else may be affected by aberrant gene regulation resulting from mutations in
817   replication and chromatin factors. In either case, the target genes mis-regulated in these
818   syndromes, if they can be identified, may provide useful evolutionary markers to distinguish
819   convergent from homologous patellar status.

820   Developmental studies in mouse or chick embryos, sometimes with induced paralysis, document
821   the additional importance of local environmental factors in patellar ontogenesis (Hosseini &
822   Hogg 1991; Mikic et al. 2000; Nowlan et al. 2010a; Nowlan et al. 2010b; Osborne et al. 2002;
823   Rot-Nikcevic et al. 2006). Similarly, embryonic development and hindlimb activity in the case of
824   particular marsupials may be important in understanding the diversity of patellar states in this
825   group. A better understanding of these environmental processes will also be helpful to disentangle
826   genomic versus epigenomic regulation of patellar development, and hence evolution.

827   CONCLUSIONS

828   *How "the mammalian patella" evolved*
829   The widespread, repeated evolution of the bony patella across evolution argues for an important
830   role in locomotor biomechanics. In animals lacking an ossified patella (e.g. Lissamphibia,
831   Testudines, Crocodylia; as well as many extinct lineages of tetrapods), the consequences of this
832   ancestral absence for hindlimb function remain mostly unstudied. This mystery is striking, in
833   particular, within Mammalia where most marsupials lack an ossified patella, as did numerous
834   fossil stem-mammals, despite seeming to share common ecological niches and the associated
835   locomotor requirements. This sporadic occurrence in marsupials and stem mammals contrasts
836   with its near universality and evolutionary stability in the Eutheria as noted above.

837   The exact number of independent origins of a bony patella among mammals remains unclear, but
838   we have estimated at least four convergent episodes inside Mammaliaformes, and several
839   instances of patellar "loss" (with apparent re-gain in some marsupials). The pattern of acquisition

840 and loss will require revisiting as new fossil material is discovered, as our evolutionary
841 reconstructions are dependent on single specimens for many ancient taxa. Moreover, patellar
842 status has not been verified for all >5,000 eutherian and >330 metatherian species (Wilson &
843 Reeder 2005), so it is possible that additional placental species (other than the fully aquatic
844 forms) may be found lacking, or marsupials having, a bony patella. A recent evolutionary study
845 documented many apparently independent evolutionary origins of the caecal appendix in
846 mammals; thus the convergent evolution of unusual anatomical structures like the osseous patella
847 has precedent (Smith et al. 2013). Similarly, blue coloration among tarantula spiders apparently
848 involved at least eight independent evolutionary acquisitions, among different microscopic
849 anatomical structures affecting spectral reflectance and hence general external colour (Hsiung et
850 al. 2015). A better understanding of the genomic signatures required for development of such
851 novel structures should be very helpful to deconstruct the observed complex patterns of
852 evolution, distinguishing between convergent evolution (homoplasy) and shared inheritance
853 (synapomorphy/homology).

854 Given that the patella evolved, and was also lost, multiple times in mammals and other Tetrapoda
855 (Fig. 3), one thing is clear. Much as we have referred to "the patella" throughout this study, there
856 is no such thing—perhaps not even a single "mammalian patella". The story of patellar evolution
857 is one of many (bony) patellae; a story of diverse evolutionary origins as well as forms, functions,
858 ontogenies and perhaps even diverse underlying genetics. Mottershead (1988) wondered if the
859 patella is "not typical of its kind" for a sesamoid bone (Mottershead 1988). Yet even patellae are
860 not necessarily typical for patellae, let alone other sesamoids-- there are double or fatty patellae
861 in some birds (Regnault et al. 2014), proximal suprapatellae and/or fibrocartilaginous patelloids
862 in many marsupials, no ossified (or even other forms of) patellae in many species, and even
863 amongst those animals that have patellae, there are numerous shapes and sizes of patellae (Figs.
864 4,S1-S3), suggesting still-unappreciated lifestyle constraints in patellar (and knee joint)
865 mechanics.

866 While we have provisionally used the terms "patelloid" and "suprapatella" for non-ossified
867 tissues near where the patella is or might be found, the validity of these terms needs further
868 inspection in a broader context. Certainly, patellae exist in non-ossified forms in younger animals
869 before endochondral ossification completes, and where such ossification does not initiate at all
870 during ontogeny it may be best to apply the term "patella" to such tissues rather than invoke new
871 terms for the same organ that simply underwent different tissue development; as above, a case of
872 divergent character state transformation rather than distinct characters (i.e. new organs). This is
873 not simply a semantic issue as the implications for evolutionary novelty, adaptation and "evo-
874 devo" of patella-like structures will depend on the decisions made about homology of these traits
875 in organisms, and how those decisions are communicated by the choice of anatomical
876 terminology.

877 *Future prospects*
878 Our discussion of patellar evolution in Mammalia has identified several areas where key
879 questions remain unresolved, in addition to uncertainties about the amount of
880 convergence/parallel evolution in origins of the osseous patella and about specific roles of (and
881 interactions between) genetic/developmental factors in bony patellar formation/loss. Considering
882 that mechanical loads are known to play an important role in the development of sesamoid bones
883 (in particular in early ontogeny), studies linking these loads to genetic/developmental control as
884 well as broad evolutionary patterns could prove very insightful, especially in explaining the
885 seemingly large amount of patellar homoplasy in mammalian evolution. Mammals may be less

886   sensitive (i.e. more genetically assimilated (e.g. Vickaryous & Olson 2007)) than birds in terms
887   of the relative influence of mechanical loads on bone (including sesamoid) ontogeny (Nowlan et
888   al. 2010b) -- this idea deserves better testing as insight into load-based influences improves.
889   Furthermore, indications that some bones within an organism may be more responsive to their
890   loading regime (Nowlan et al. 2010a) may be of great relevance to interpreting patellar biology
891   and evolution, but at present strong inferences cannot be drawn about how variable the patella's
892   responsiveness to mechanics is within or among organisms. There is clearly much room for
893   further study of the patellae of mammals and other tetrapods, and here we have noted directions
894   in which these might most beneficially be directed.

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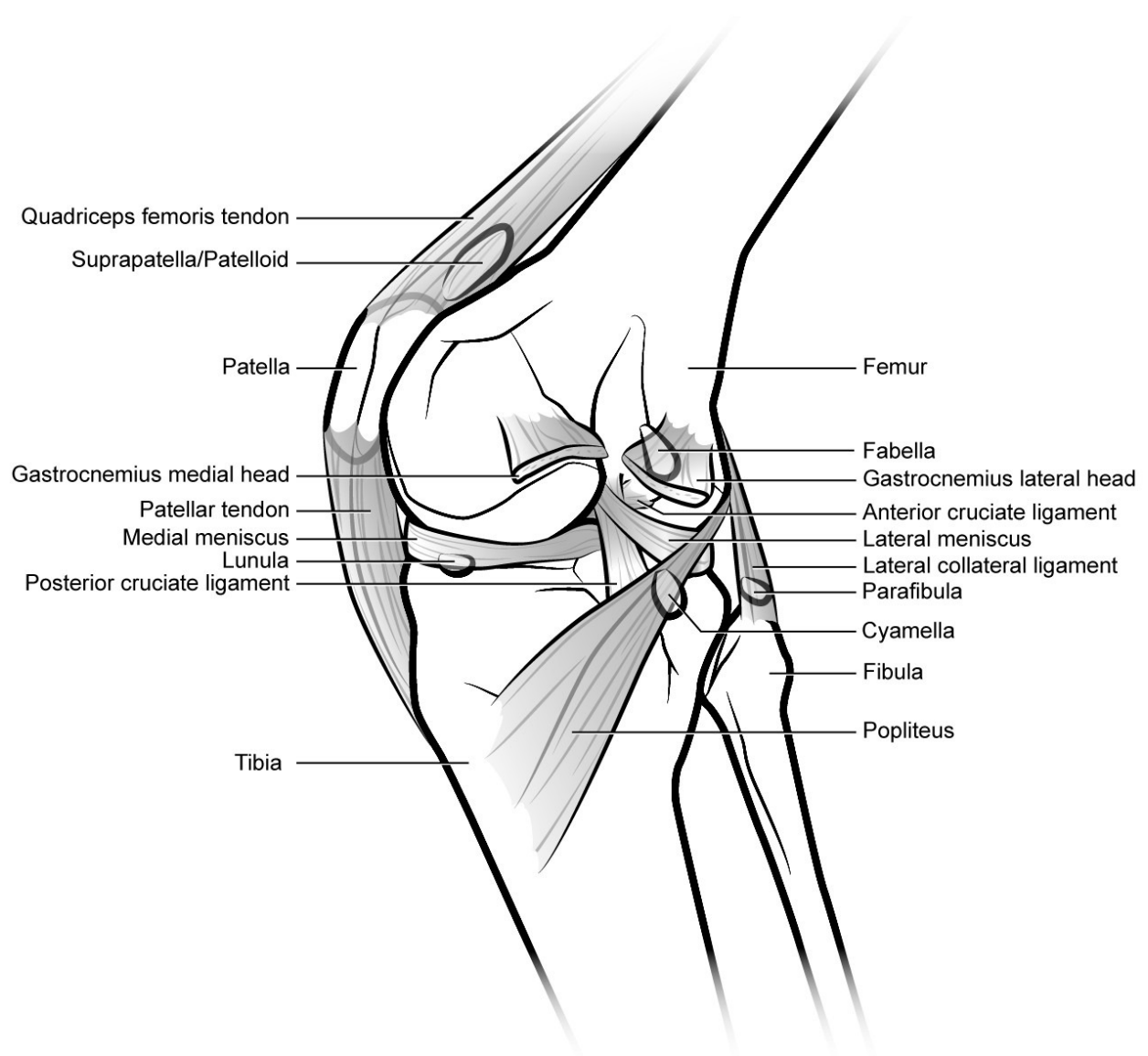
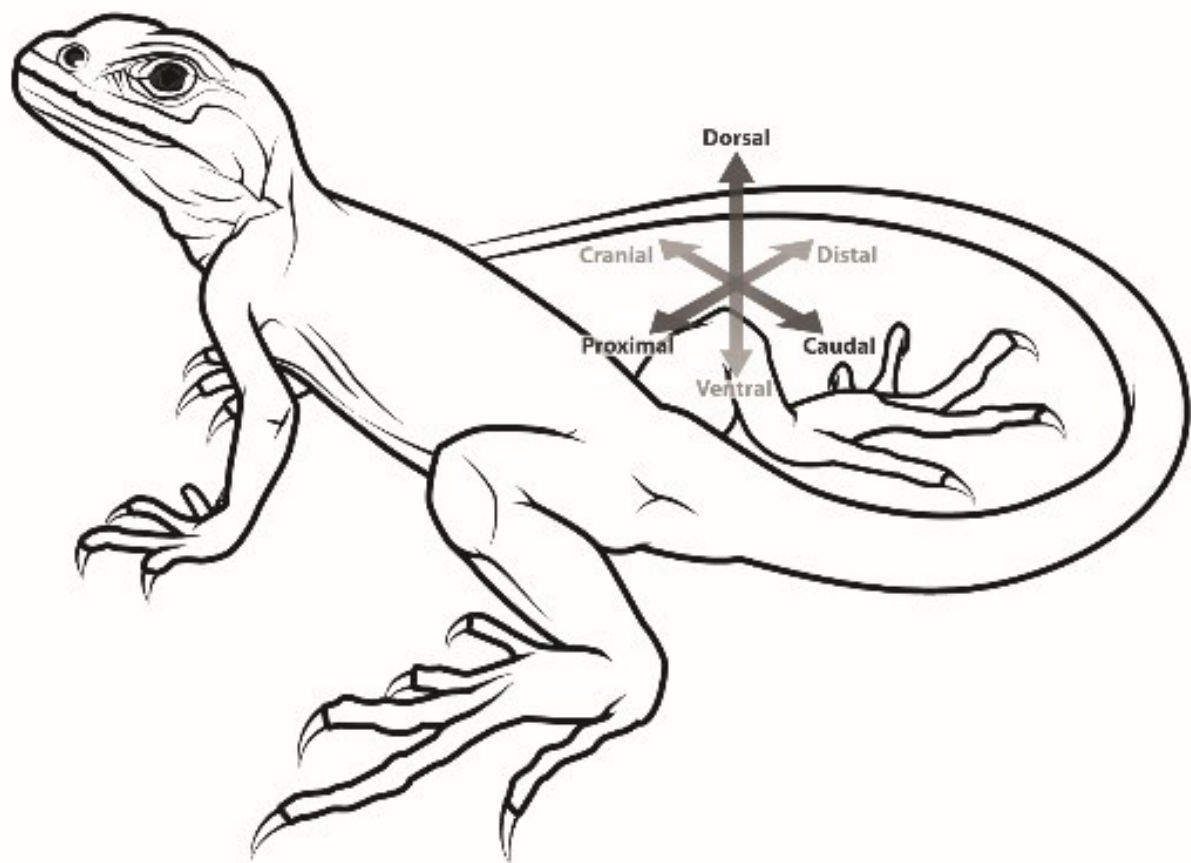
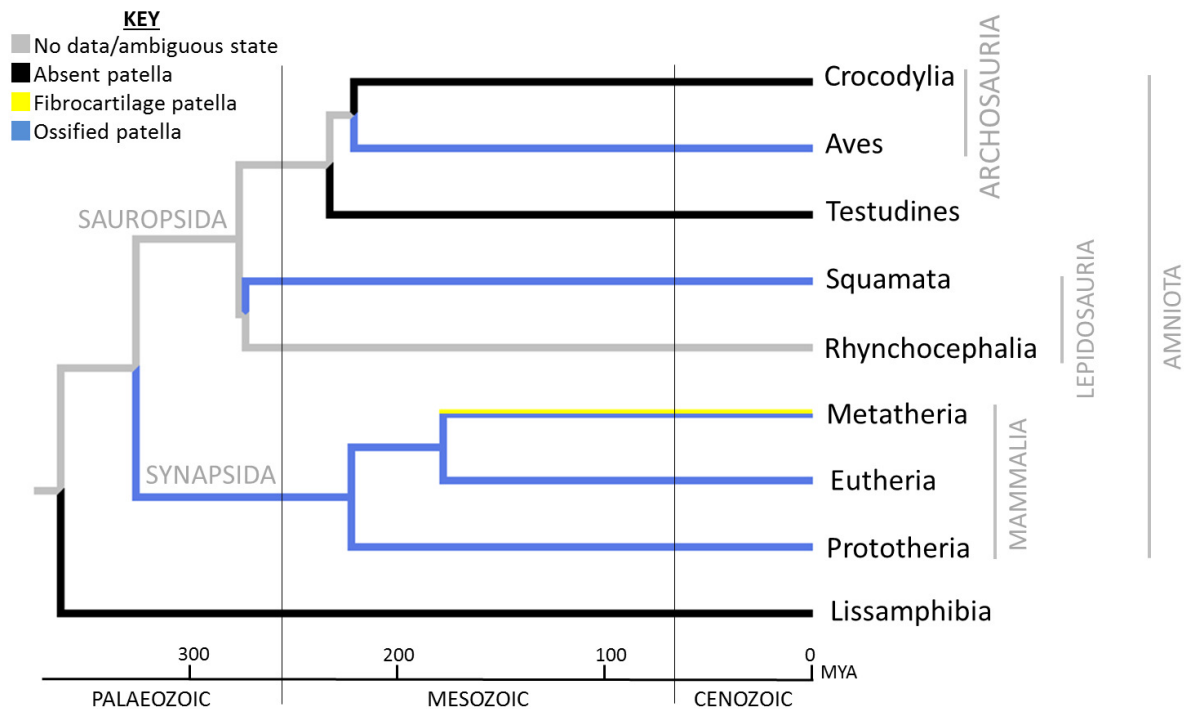
1483   FIGURES

1484   Figure 1. Generalized knee showing sesamoid bones found in various mammals, although
1485   possibly no species includes all of these (patella, lunula, cyamella, fabella and parafibula). Also
1486   shown are relevant muscles, ligaments and other anatomical elements that lie close to the
1487   sesamoids of the knee joint. The knee is in medial view and the medial collateral ligament has
1488   been removed. Illustration: Manuela Bertoni.

1489   Figure 2. Generalized tetrapod with anatomical/developmental axes defined for the hindlimb:
1490   cranial/caudal (towards the head/tail respectively), proximal/distal (toward/further from the trunk
1491   respectively), dorsal/ventral (towards the back/belly respectively). Illustration: Manuela Bertoni.

1492   Figure 3. Reconstruction of ancestral patellar states in Tetrapoda, showing the major extant
1493   clades. Reconstruction was performed using Mesquite's parsimony algorithm and unordered
1494   character states, where 0 (black) = absent patella, 1 (yellow) = soft tissue patella/patelloid, and 2
1495   (blue) = ossified patella; see Methods for further details. The distribution of the ossified patella
1496   among extant clades has been interpreted as three occasions of independent evolution (in Aves,
1497   Squamata, and Mammalia) (Dye, 1987, Haines, 1940), a conclusion strongly reinforced by
1498   specific fossil evidence (absence or equivocality of a patella in all outgroups). Reconstruction
1499   within Mammalia is explored in more depth in Figures 5-7. MYA= millions of years from
1500   present.

1501   Figure 4. Examples of tetrapods with or without patellae. Red arrows denote the patella. A, B.
1502   *Ornithorhynchus anatinus* (Monotremata: duck-billed platypus, Redpath Museum specimen
1503   2458). C, D. *Tachyglossus aculeatus* (Monotremata: echidna, Redpath Museum specimen 2463).
1504   E, F. *Didelphis virginiana* (Metatheria: North American opossum, Redpath Museum specimen
1505   5019). G, H. *Procavia capensis* (Eutheria: Afrotheria: Cape hyrax, uncatalogued Horniman
1506   Museum specimen, London, United Kingdom). I, knee of patient with Meier-Gorlin Syndrome
1507   (Guernsey et al. 2010). For more images of mammalian patellae (or lack thereof in some
1508   marsupials), see Figures S1-S3.

A

B

C

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E

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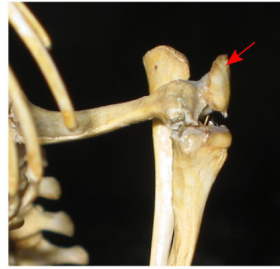
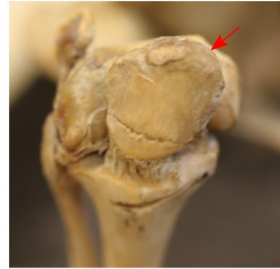
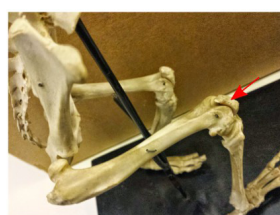
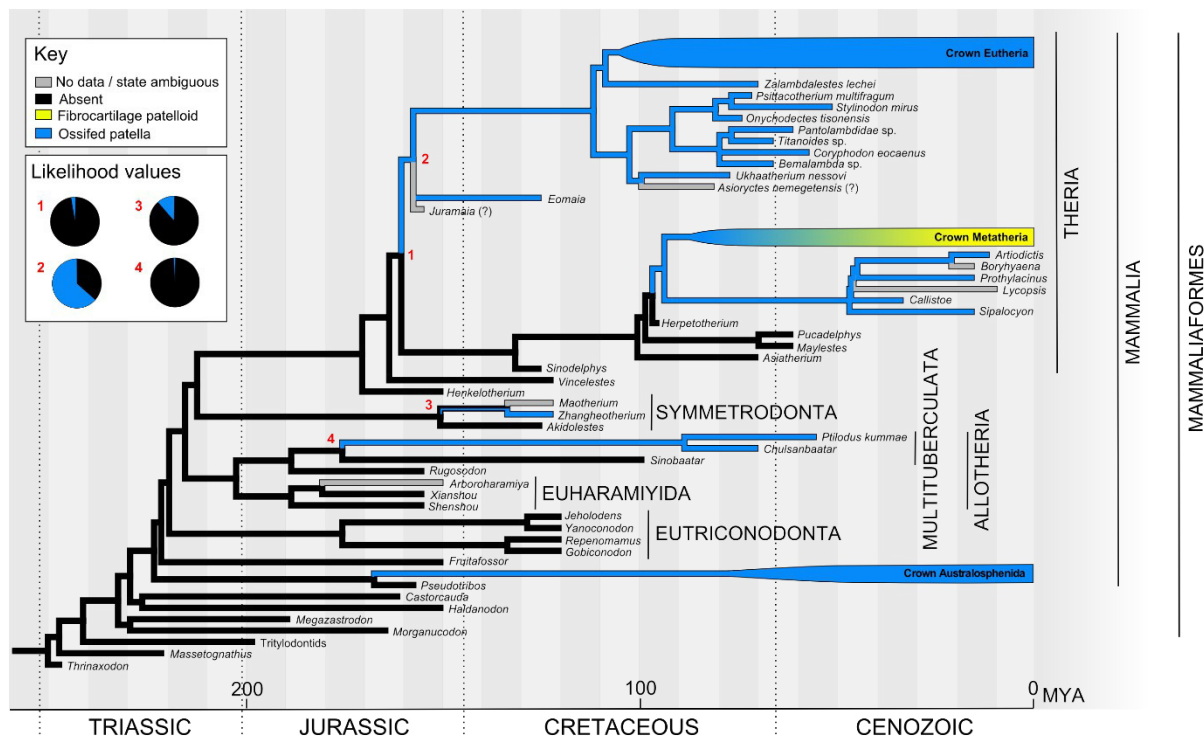
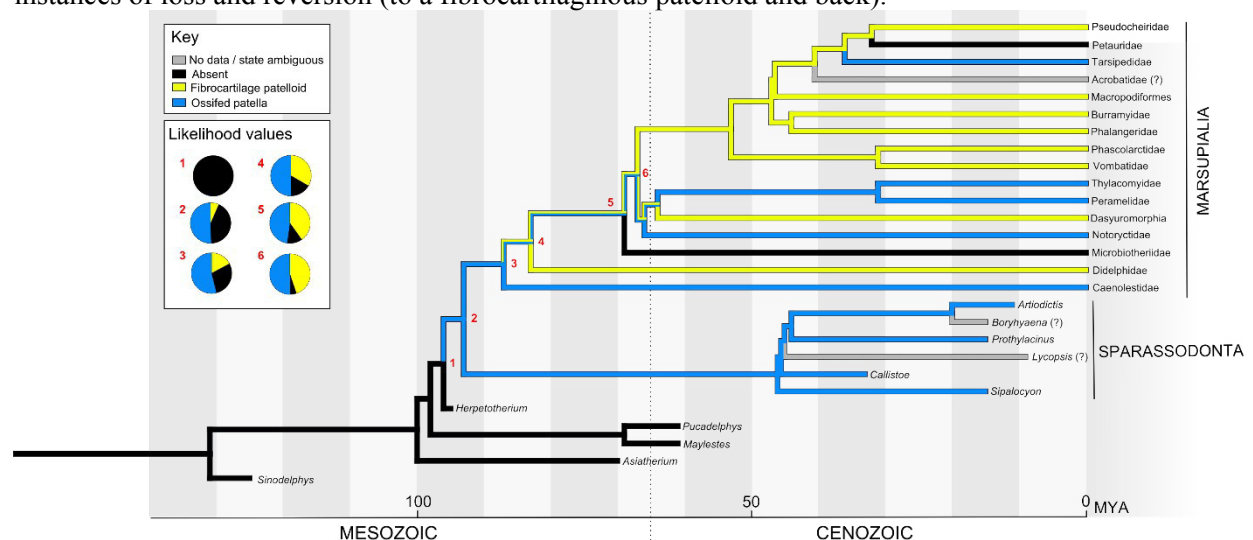

1509   Figure 5. Ancestral state reconstruction of the patella in Mesozoic mammals (see Fig. S4 for alternative
1510   tree topology). Key fossils with hindlimb material are denoted by †. The main tree shows a parsimony
1511   reconstruction using unordered character states, where branch colour indicates reconstructed state.
1512   Maximum likelihood gives similar results to parsimony, and likelihood values for numbered nodes are
1513   displayed (inset). Crown Metatheria and Eutheria are further explored in Figs. 6 and 7. Our results suggest
1514   that the ossified patella has evolved at least five times within Mammaliaformes.

1515 Figure 6. Ancestral state reconstruction of the patella in Metatheria and related taxa. Key fossils with
1516 hindlimb material are denoted by †. The main tree shows a parsimony reconstruction using unordered
1517 character states, where branch colour indicates reconstructed state. Likelihood values for the numbered
1518 nodes are shown (inset). Our results suggest that the ossified patella evolved once in Metatheria, with
1519 instances of loss and reversion (to a fibrocartilaginous patelloid and back).

1520   Figure 7. Ancestral state reconstruction of the patella in Eutheria. Key fossils with hindlimb material are
1521   denoted by †. The main tree shows a parsimony reconstruction using unordered character states, where
1522   branch colour indicates the reconstructed state. Our results suggest that the ossified patella evolved only
1523   once within Eutheria and (as far as is currently known) has only been lost by the bat genus *Pteropus* (not
1524   counting groups which have lost hindlimbs; e.g. *Trichechus manatus*/crown Sirenia, *Tursiops*
1525   *truncatus*/crown Cetacea).

Key
- No data / state ambiguous
- Absent
- Fibrocartilage patelloid
- Ossified patella

Tursiops truncatus — CETACEA

Basilosaurus isis
Dorudon atrox
Artiocetus clavis
Rodhocetus balochistanensis
Maiacetus inuus
Pakicetus attocki (?)
Ambulocetus natans
Indohyus sp.
Gervachoerus jaegeri
Diacodexis metsiacus
Archaeotherium sp.
Bos taurus
Leptomeryx evansi
Elomeryx armatus
Protoreodon annectens
Camelus dromedarius
Merychyus major
Caenotherium sp.
Paratylopus sternbergi

CETARTIODACTYLA

Propalaeotherium hassiacum
Plesippus shoshonensis
Mesohippus grallipes
Equus ferus caballus
Archaeohippus ultimus
Hyracotherium grangeri
Embolotherium andrewsi
Aktautitan hippopotamops
Megacerops tyleri
Palaeosyops paludosus
Subhyracodon mitis
Rhinoceros unicornis
Paraceratherium sp.
Hyrachyus sp.
Litolophus gobiensis
Toxodon sp. — NOTOUNGULATA
Allalmeia atalaensis
Eoauchenia sp.
Paleoparadoxia sp.
Desmostylus hesperus — DESMOSTYLIA

PERISSODACTYLA

Tetraclaenodon puercensis
Copecion brachypterus
Phenacodus intermedius
Meniscotherium robustum
Uintatherium anceps — DINOCERATA
Prodinoceras sp.
Pachyaena ossifraga
Pachyaena gracilis
Mesonyx obtusidens
Hyopsodus paulus

PHENACODONTIDAE

MESONYCHIA

Mioclaenus sp.
Chriacus sp.
Arctocyon primaevus
Protungulatum donnae (?)
Lasiurus borealis
Carollia perspiculata
Tachypteron franzeni
Pteropus spp
Cynopterus brachyotis
Icaronycteris index
Onychonycteris finneyi

CHIROPTERA

Smilodon fatalis
Felis catus
Pogonodon brachyops
Hoplophoneus primaevus
Canis familiaris
Ursus maritimus
Brachypsalis modicus
Phoca vitalina

CARNIVORA

Vulpavus ovatus
Paroodectes feisti
Miacis spp. (?) — MIACIDAE
Patriofelis sp.
Oxyaena sp.
Hyaenodon gigas — CREODONTA
Arfia shoshoniensis
Emanodon antelios
Brachianodon westorum — PALAEANODONTA
Alocodontulum atopum
Eomanis waldi
Manis pentadactyla — PHOLIDOTA

Talpa europaea
Erinaceus europaeus
Homo sapiens
Homo neanderthalensis
Australopithecus robustus
Australopithecus afarensis
Pan troglodytes
Gorilla gorilla
Pongo sp.
Pierolapithecus catalaunicus
Nacholapithecus kerioi
Proconsul spp.
Oreopithecus sp.
Pliopithecus sp.

PRIMATES

Archicebus achilles
Teilhardina belgica (?)
Omomys sp.
Loris lydekkerianus
Pelycodus jarrovii
Notharctus spp.
Darwinius masillae
Plesiadapis cookei
Tupaia tana
Cynocephalus volans

NOTHARCTIDAE

Apatemys chardini
Nonanomalurus soniae
Sciurus carolinensis
Castoroides ohioensis
Pseudotomus eugenei
Paramys delicatus
Ischyromys sp.
Lepus americanus
Hypolagus beremendensis
Rhombomylus turpanensis
Trichechus manatus

GLIRES

EUARCHONTOGLIRES

Protosiren sp.
Pezosiren portelli
Moeritherium sp.
Loxodonta africana
Mammuthus sp.
Mammut americanum
Numidotherium koholensis
Arsinoitherium zitteli
Carodnia vieira
Procavia capensis
Orycteropus afer
Macroscelides proboscideus
Leptictidium nasutum
Tenrec ecaudatus
Trachycalyptus sp.
Dasypus novemcinctus
Myrmecophaga tridactyla — XENARTHRA
Choloepus didactylus

AFROTHERIA

Zalambdalestes lechei
Psittacotherium multifragum
Stylinodon mirus — TAENIODONTA
Onychodectes tisonensis
Pantolambdidae sp.
Titanoides sp.
Coryphodon eocaenus — PANTODONTA
Bemalambda sp.
Ukhaatherium nessovi
Asioryctes nemegetensis (?)

LAURASIATHERIA

100 — 50 — 0 MYA

MESOZOIC — CENOZOIC